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(54) Title: **NUCLEIC ACID SEQUENCES FROM DROSOPHILA MELANOGASTER THAT ENCODE PROTEINS ESSEN-  
TIAL FOR LARVAL VIABILITY AND USES THEREOF**

(57) Abstract: Nucleotide sequences are isolated from *Drosophila melanogaster* that code for proteins essential for larval viability. These proteins are useful for discovering new insecticides based on the essentiality of the nucleotide sequences for *Drosophila* larval viability. Further provided are recombinant proteins and methods for identifying inhibitors to these proteins. Protein inhibitors active in the methods disclosed herein are useful as insecticidal, ectoparasitocidal, antiparasitic, anthelmintic and acaricidal agents.



**WO 02/057455 A2**

# NUCLEIC ACID SEQUENCES FROM *DROSOPHILA MELANOGASTER* THAT ENCODE PROTEINS ESSENTIAL FOR LARVAL VIABILITY AND USES THEREOF

This application claims the benefit of U.S. Provisional Application No. 60/262,351, filed January 18, 2001, incorporated herein by reference.

## FIELD OF INVENTION

The present invention pertains to nucleic acid sequences isolated from *Drosophila melanogaster* that encode proteins essential for larval viability. The invention particularly relates to methods of using these proteins as insecticide targets, based on this essentiality.

## BACKGROUND OF THE INVENTION

Insects contribute or cause many human and animal diseases, and are responsible for substantial agricultural and property damage. The societal costs associated with insect pests in dollars, time and suffering are monumental. The total worldwide market size for insecticide crop protection is over \$5 billion. To combat these problems, insecticidal compounds have been developed and employed.

The idea to use chemicals for insect control is not new. The scientific use of pesticides started with the introduction of arsenical insecticides and organic compounds such as tar, petroleum oils, and dinitrophenol emulsions at the end of the last century. But, the systematic search for synthetic organic insecticides was only launched after the discovery of the insecticidal properties of DDT in 1939. After World War II, chemical research concentrated mainly on chlorinated hydrocarbons and cyclodienes, which all require high rates of application and have a rather broad spectrum of activity. Most of them are persistent in the environment and may pose a significant risk for accumulation in the food chain. Today the use of these chemicals is very much restricted.

From this point, the major emphasis in research has been given to organophosphates and carbamates, which are readily degradable in the environment with little tendency for bioaccumulation. The toxicity of these compounds varies within a broad range from medium to highly toxic. Organophosphates and carbamates are still widely use, although the more

toxic ones are banned in certain countries. The formamidines have as their major advantage a different mode of action and their selectivity, which made them suitable for use in IPM (insect pest management) programs. They are easily degradable with no accumulation potential, but for toxicological reasons some have had to be withdrawn from the market.

For the past decade, insecticide research has concentrated on leadfinding for new chemical structures interfering with new target mechanisms. The chances for success are rather remote, because the hurdles for the registration of a new insecticide are set very high. Toxicological aspects, insecticide resistance, environmental behavior, and IPM fitness are some of the critical factors that have to be considered together with economical factors.

Novel insecticides can now be discovered using high-throughput screens that implement recombinant DNA technology. Proteins found to be essential to insect viability can be recombinantly produced through standard molecular biological techniques and utilized as insecticide targets in screens for novel inhibitors of the enzymes' activity. The novel inhibitors discovered through such screens may then be used as insecticides to control undesirable insect infestation.

However, as the world population continues to grow, there will be increasing food shortages. Therefore, there exists continuing need to find new, effective and economic insecticides.

## SUMMARY OF THE INVENTION

In view of these needs, it is one object of the invention to provide essential genes in insects such as *Drosophila melanogaster*. It is another object to provide the essential proteins encoded by these essential genes for assay development to identify inhibitory compounds with insecticidal activity. It is still another object of the present invention to provide an effective and beneficial method for identifying new or improved insecticides using the essential proteins of the invention.

In furtherance of these and other objects, the present invention provides DNA molecules comprising nucleotide sequences isolated from *Drosophila melanogaster* that encode proteins essential for larval viability. The inventors are the first to demonstrate that the nucleotide sequences of the invention are essential for larval viability. This knowledge is exploited to provide novel insecticide modes of action. One advantage of the present

invention is that the proteins encoded by the essential nucleotide sequences provide the bases for assays designed to easily and rapidly identify novel insecticides.

Disruption of the nucleotide sequences of the invention demonstrates that the activity of each corresponding encoded protein is essential for *Drosophila* larval viability. Genetic results show that when each nucleotide sequence of the invention is mutated in *Drosophila*, the resulting phenotype is larval lethal in the homozygous state. This demonstrates a critical role for the protein encoded by the mutated nucleotide sequence. This further implies that chemicals that inhibit the expression of the protein when in contact with insects are likely to have detrimental effects on insects and are potentially good insecticide candidates. The present invention therefore provides methods of using the disclosed nucleotide sequences or proteins encoded thereby to identify inhibitors thereof. The inhibitors can then be used as insecticides to kill undesirable insect populations where crops are grown, particularly agronomically important crops such as maize, and other cereal crops such as wheat, oats, rye, sorghum, rice, barley, millet, turf and forage grasses and the like, as well as cotton, sugar cane, sugar beet, oilseed rape, soybeans, vegetable crops and fruits.

The present invention accordingly provides cDNA sequences derived from *Drosophila melanogaster*. In one embodiment, the present invention provides an isolated DNA molecule comprising a nucleotide sequence selected from the group consisting of the odd numbered SEQ ID NOs:1-73. In another embodiment, the present invention provides an isolated DNA molecule comprising a nucleotide sequence that encodes a protein selected from the group consisting of the even numbered SEQ ID NOs:2-74.

The present invention also provides a chimeric construct comprising a promoter operatively linked to a DNA molecule according to the present invention, wherein the promoter is preferably functional in a eukaryote, wherein the promoter is preferably heterologous to the DNA molecule. The present invention further provides a recombinant vector comprising a chimeric construct according to the present invention, wherein said vector is capable of being stably transformed into a host cell. The present invention still further provides a host cell comprising a DNA molecule according to the present invention, wherein said DNA molecule is preferably expressible in the cell. The host cell is preferably selected from the group consisting of an insect cell, a yeast cell, and a prokaryotic cell.

The present invention also provides proteins essential for *Drosophila melanogaster* larval viability. In one embodiment, the present invention provides an isolated protein comprising an amino acid sequence selected from the group consisting of the even numbered



SEQ ID NOs:2-74. In accordance with another embodiment, the present invention also relates to the recombinant production of proteins of the invention and methods of using the proteins of the invention in assays for identifying compounds that interact with the protein.

In another preferred embodiment, the present invention describes a method for identifying chemicals having the ability to inhibit the activity of the disclosed proteins. In a preferred embodiment, the present invention provides a method for selecting compounds that interact with a protein of the invention, comprising: (a) expressing a DNA molecule according to the present invention to generate the corresponding protein of the invention, (b) testing a compound suspected of having the ability to interact with the protein expressed in step (a), and (c) selecting compounds that interact with the protein in step (b).

Other objects and advantages of the present invention will become apparent to those skilled in the art and from a study of the following description of the invention and non-limiting examples. The entire contents of all publications mentioned herein are hereby incorporated by reference.

#### BRIEF DESCRIPTION OF THE SEQUENCES IN THE SEQUENCE LISTING

Odd numbered SEQ ID NOs:1-73 are nucleotide sequences described in the table below.

Even numbered SEQ ID NOs:2-74 are protein sequences encoded by the immediately preceding nucleotide sequence, e.g., SEQ ID NO:2 is the protein encoded by the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:4 is the protein encoded by the nucleotide sequence of SEQ ID NO:3, etc.

SEQ ID NOs:75-87 are PCR primers.

SEQ ID NO:	CT	Gene Name	BLAST
1	CT10671	SUH	geminin L [Xenopus laevis] 4e-06
3	CT11789		Expect = 0 Score = 735 gi 1477785 (U60093) suppressor of hairless protein 1 [Xenopus laevis]
5	CT12299		6016932 Expect = 1.e-110 Score = 777 gi 6016932 emb CAB57836.1  (AL031667) dJ620E11.1a (novel Helicase C-terminal domain and SNF2 N-termi
7	CT12433	NOT	F5M15.23 [Arabidopsis] 5e-11
9	CT13750		KIAA1063 protein [Homo sapiens] e-137
11	CT14668		Expect = 1.e-06 Score = 56.2 gi 4008434 emb CAA21644.1  (AL032640) predicted using Genefinder; cDNA EST yk416g4.5 comes from this
13	CT14840		gi 5051628 gb AAD38322.1 AF047033_1 (AF047033) sodium bicarbonate cotransporter 3 [Homo sapiens]
15	CT14856		gi 7503817 pir T22427 hypothetical protein F49C5.4 - Caenorhabditis elegans >gi 3877329 emb CAB04433.1  (Z81544) contains similarity to Pfam domain: PF00069 (Eukaryotic protein kinase domain), Score=306.1, E-value=1.4e-88, N=1 [Caenorhabditis elegans] Score = 277 bits (702), Expect = 2e-73
17	CT1649		Y09022 g1653999 Human mRNA for Not56-like protein.
19	CT17906		M. musculus 1168457 Expect = 1.e-24 Score = 415.7 gi 1168457 sp Q02357 ANK1_MOUSE ANKYRIN >gi 2119259 pir I49502 ankyrin - mouse >gi 191940 (M84756)
21	CT18206		synaptotagmin 5 [Homo sapiens] 2.3
23	CT19380		
25	CT19738	TARA	
27	CT20428	CNK	Expect = 2.e-47 Score = 264.2 gi 4151807 gb AAD04568.1  (AF102854) membrane-associated guanylate kinase-interacting protein 2 Magu
29	CT20708	AGO1	C. elegans 3877299 Expect = 0 Score = 1256 gi 3877299 emb CAA93496.1  (Z69661) cDNA EST EMBL:D70203 comes from this gene; cDNA EST EMBL:D71003
31	CT21945	DUP	gi 7573546 emb CAB87836.1  (AJ250122) putative CDT1 protein [Xenopus laevis] Score = 241 bits (609), Expect = 2e-62
33	CT22383	GLYP	Expect = 0 Score = 1252 gi 1836054 bbs 179296 (S82859) alpha-1,4-glucan orthophosphate glycosyl transferase, myophosphorylas
35	CT22943	OSA	SWIILbeta protein [Homo sapiens] 2e-72
37	CT23155	MCR	KIAA1283 protein [Homo sapiens] 9e-05
39	CT23802		Expect = 1.e-118 Score = 425 gi 2645879 (AF034374) molybdenum cofactor biosynthesis protein A [Homo sapiens]
41	CT2428		Expect = 7.e-24 Score = 186.6 gi 3878582 emb CAB01235.1  (Z77667) predicted using

43	CT25884		Genefinder; similar to zinc-finger protein; cDNA gi 6648069 sp P50544 ACDV_MOUSE ACYL-COA DEHYDROGENASE, VERY-LONG-CHAIN SPECIFIC, MITOCHONDRIAL PREC
45	CT26690	XBP1	Remainders 2118500 Expect = 7.e-12 Score =73.4 gi 2118500 pir  JC4857 hepatocarcinogenesis-related transcription factor - rat >gi 5596360 dbj BAA82
47	CT27692		Expect = 2.e-16 Score =87.4 gi 465731 sp P34276 YKJ2_CAEEL HYPOTHETICAL 36.9 KD PROTEIN C02D5.2 IN CHROMOSOME III >gi 630504 pir , 1.e-05 51.5 gi 5453696 ref NP_006323.1   interferon, gamma- inducible protein 30 >gi 124495 sp P13284 INP_HUMAN
49	CT28625	NOP5	H. sapiens 4680298 Expect = 1.e-Score =144 535.9 gi 4680298 gb AAD27610.1 AF123534_1 (AF123534) nucleolar protein NOP5/NOP58 [Homo sapiens]
51	CT28865	HOW	C. elegans 1947005 Expect =5.e-75 Score =282 gi 1947005 (AF000197) similar to C. elegans female germline-specific tumor suppressor GLD-1 (SP:G841
53	CT29244		Sil1 protein [Mus musculus] 7e-31
55	CT29824	RPL30	Expect =4.e-45 Score =180 gi 4506631 ref NP_000980.1   ribosomal protein L30 >gi 6677783 ref NP_033109.1   ribosomal protein L
57	CT34960		
59	CT36603	Ubi-p63E	Expect =1.e-21 Score =202 gi 84834 pir  JH0302 polyubiquitin - tobacco hornworm (fragments)
61	CT37944		M. musculus 2494763 Expect =0 Score =783 gi 2494763 sp P70698 PYRG_MOUSE CTP SYNTHASE (UTP--AMMONIA LIGASE) (CTP SYNTHETASE) >gi 1515357 (U49 H. sapiens 4503133-0 783 gi 4503133 ref NP_001896.1   CTP synthase; cytidine 5-prime triphosphate synthetase >gi 131735 sp P1
63	CT38280	SNF4A&G GR	AMP-activated protein kinase gamma2 subunit [Homo sapiens] e-110
65	CT9393	BcDNA:G H08860	Expect =5.e-86 319 gi 730984 sp P40387 TPS1_SCHPO ALPHA, ALPHA-TREHALOSE-PHOSPHATE SYNTHASE [UDP-FORMING] (TREHALOSE-6-P 2.4 Y16752 g3757660 Human mRNA for secretagogen, complete cds. 0
67	GH22170		
69	GM02843		9 AF047437 g3335129 Human sperm acrosomal protein mRNA, complete cds. 0
71	GM03018		0.03 MATERNAL PUMILIO PROTEIN >gi 103349 pir  S22026 pumilio protein - fruit fly (Drosophila melanogaster) >gi 8394 emb CAA44474  (X62589) pumilio [Drosophila melanogaster]
73	UNI1	UNI1	

## DEFINITIONS

For clarity, certain terms used in the specification are defined and used as follows:

“Associated with / operatively linked” refer to two nucleic acid sequences that are related physically or functionally. For example, a promoter or regulatory DNA sequence is said to be “associated with” a DNA sequence that codes for an RNA or a protein if the two sequences are operatively linked, or situated such that the regulator DNA sequence will affect the expression level of the coding or structural DNA sequence.

A “chimeric construct” is a recombinant nucleic acid sequence in which a promoter or regulatory nucleic acid sequence is operatively linked to, or associated with, a nucleic acid sequence that codes for an mRNA or which is expressed as a protein, such that the regulatory nucleic acid sequence is able to regulate transcription or expression of the associated nucleic acid sequence. The regulatory nucleic acid sequence of the chimeric construct is not normally operatively linked to the associated nucleic acid sequence as found in nature.

Co-factor: natural reactant, such as an organic molecule or a metal ion, required in an enzyme-catalyzed reaction. A co-factor is e.g. NAD(P), riboflavin (including FAD and FMN), folate, molybdopterin, thiamin, biotin, lipoic acid, pantothenic acid and coenzyme A, S-adenosylmethionine, pyridoxal phosphate, ubiquinone, menaquinone. Optionally, a co-factor can be regenerated and reused.

A “coding sequence” is a nucleic acid sequence that is transcribed into RNA such as mRNA, rRNA, tRNA, snRNA, sense RNA or antisense RNA. Preferably the RNA is then translated in an organism to produce a protein.

Complementary: “complementary” refers to two nucleotide sequences that comprise antiparallel nucleotide sequences capable of pairing with one another upon formation of hydrogen bonds between the complementary base residues in the antiparallel nucleotide sequences.

“Conservatively modified variations” of a particular nucleic acid sequence refers to those nucleic acid sequences that encode identical or essentially identical amino acid sequences, or where the nucleic acid sequence does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given polypeptide. For instance the codons CGT, CGC, CGA, CGG, AGA, and AGG all encode the amino acid arginine. Thus, at every position where an arginine is specified by a codon, the codon can be altered to any of the

corresponding codons described without altering the encoded protein. Such nucleic acid variations are "silent variations" which are one species of "conservatively modified variations." Every nucleic acid sequence described herein which encodes a protein also describes every possible silent variation, except where otherwise noted. One of skill will recognize that each codon in a nucleic acid (except ATG, which is ordinarily the only codon for methionine) can be modified to yield a functionally identical molecule by standard techniques. Accordingly, each "silent variation" of a nucleic acid which encodes a protein is implicit in each described sequence.

Furthermore, one of skill will recognize that individual substitutions deletions or additions that alter, add or delete a single amino acid or a small percentage of amino acids (typically less than 5%, more typically less than 1%) in an encoded sequence are "conservatively modified variations," where the alterations result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. The following five groups each contain amino acids that are conservative substitutions for one another: Aliphatic: Glycine (G), Alanine (A), Valine (V), Leucine (L), Isoleucine (I); Aromatic: Phenylalanine (F), Tyrosine (Y), Tryptophan (W); Sulfur-containing: Methionine (M), Cysteine (C); Basic: Arginine (R), Lysine (K), Histidine (H); Acidic: Aspartic acid (D), Glutamic acid (E), Asparagine (N), Glutamine (Q). *See also*, Creighton (1984) *Proteins*, W.H. Freeman and Company. In addition, individual substitutions, deletions or additions which alter, add or delete a single amino acid or a small percentage of amino acids in an encoded sequence are also "conservatively modified variations."

**DNA Shuffling:** DNA shuffling is a method to rapidly, easily and efficiently introduce mutations or rearrangements, preferably randomly, in a DNA molecule or to generate exchanges of DNA sequences between two or more DNA molecules, preferably randomly. The DNA molecule resulting from DNA shuffling is a shuffled DNA molecule that is a non-naturally occurring DNA molecule derived from at least one template DNA molecule. The shuffled DNA encodes an enzyme modified with respect to the enzyme encoded by the template DNA, and preferably has an altered biological activity with respect to the enzyme encoded by the template DNA.

**Enzyme/Protein Activity:** means herein the ability of an enzyme (or protein) to catalyze the conversion of a substrate into a product. A substrate for the enzyme comprises the natural substrate of the enzyme but also comprises analogues of the natural substrate, which can also

be converted, by the enzyme into a product or into an analogue of a product. The activity of the enzyme is measured for example by determining the amount of product in the reaction after a certain period of time, or by determining the amount of substrate remaining in the reaction mixture after a certain period of time. The activity of the enzyme is also measured by determining the amount of an unused co-factor of the reaction remaining in the reaction mixture after a certain period of time or by determining the amount of used co-factor in the reaction mixture after a certain period of time. The activity of the enzyme is also measured by determining the amount of a donor of free energy or energy-rich molecule (e.g. ATP, phosphoenolpyruvate, acetyl phosphate or phosphocreatine) remaining in the reaction mixture after a certain period of time or by determining the amount of a used donor of free energy or energy-rich molecule (e.g. ADP, pyruvate, acetate or creatine) in the reaction mixture after a certain period of time.

Essential: an "essential" *Drosophila melanogaster* nucleotide sequence is a nucleotide sequence encoding a protein such as e.g. a biosynthetic enzyme, receptor, signal transduction protein, structural gene product, or transport protein that is essential to the growth or survival of the insect.

Expression Cassette: "Expression cassette" as used herein means a DNA sequence capable of directing expression of a particular nucleotide sequence in an appropriate host cell, comprising a promoter operatively linked to the nucleotide sequence of interest which is operatively linked to termination signals. It also typically comprises sequences required for proper translation of the nucleotide sequence. The coding region usually codes for a protein of interest but may also code for a functional RNA of interest, for example antisense RNA or a nontranslated RNA, in the sense or antisense direction. The expression cassette comprising the nucleotide sequence of interest may be chimeric, meaning that at least one of its components is heterologous with respect to at least one of its other components. The expression cassette may also be one which is naturally occurring but has been obtained in a recombinant form useful for heterologous expression. Typically, however, the expression cassette is heterologous with respect to the host, i.e., the particular DNA sequence of the expression cassette does not occur naturally in the host cell and must have been introduced into the host cell or an ancestor of the host cell by a transformation event. The expression of the nucleotide sequence in the expression cassette may be under the control of a constitutive promoter or of an inducible promoter which initiates transcription only when the host cell is exposed to some particular external stimulus. In the case of a multicellular organism, such as

an insect, the promoter can also be specific to a particular tissue or organ or stage of development.

**Gene:** the term "gene" is used broadly to refer to any segment of DNA associated with a biological function. Thus, genes include coding sequences and/or the regulatory sequences required for their expression. Genes also include nonexpressed DNA segments that, for example, form recognition sequences for other proteins. Genes can be obtained from a variety of sources, including cloning from a source of interest or synthesizing from known or predicted sequence information, and may include sequences designed to have desired parameters.

**Heterologous/exogenous:** The terms "heterologous" and "exogenous" when used herein to refer to a nucleic acid sequence (e.g. a DNA sequence) or a gene, refer to a sequence that originates from a source foreign to the particular host cell or, if from the same source, is modified from its original form. Thus, a heterologous gene in a host cell includes a gene that is endogenous to the particular host cell but has been modified through, for example, the use of DNA shuffling. The terms also include non-naturally occurring multiple copies of a naturally occurring DNA sequence. Thus, the terms refer to a DNA segment that is foreign or heterologous to the cell, or homologous to the cell but in a position within the host cell nucleic acid in which the element is not ordinarily found. Exogenous DNA segments are expressed to yield exogenous polypeptides.

A "homologous" nucleic acid (e.g. DNA) sequence is a nucleic acid (e.g. DNA) sequence naturally associated with a host cell into which it is introduced.

The terms "identical" or percent "identity" in the context of two or more nucleic acid or protein sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection.

**Inhibitor:** a chemical substance that inactivates the enzymatic activity of an enzyme (or protein) of interest. The term "insecticide" is used herein to define an inhibitor when applied to an insect at any stage of development.

**Insecticide:** a chemical substance used to kill or inhibit the growth or viability of insects at any stage of development.

Interaction: quality or state of mutual action such that the effectiveness or toxicity of one protein or compound on another protein is inhibitory (antagonists) or enhancing (agonists).

A nucleic acid sequence is "isocoding with" a reference nucleic acid sequence when the nucleic acid sequence encodes a polypeptide having the same amino acid sequence as the polypeptide encoded by the reference nucleic acid sequence.

An "isolated" nucleic acid molecule or an isolated enzyme is a nucleic acid molecule or enzyme that, by the hand of man, exists apart from its native environment and is therefore not a product of nature. An isolated nucleic acid molecule or enzyme may exist in a purified form or may exist in a non-native environment such as, for example, a recombinant host cell.

Mature Protein: protein that is normally targeted to a cellular organelle and from which the transit peptide has been removed.

Minimal Promoter: promoter elements, particularly a TATA element, that are inactive or that have greatly reduced promoter activity in the absence of upstream activation. In the presence of a suitable transcription factor, the minimal promoter functions to permit transcription.

Modified Enzyme Activity: enzyme activity different from that which naturally occurs in an insect (i.e. enzyme activity that occurs naturally in the absence of direct or indirect manipulation of such activity by man), which is tolerant to inhibitors that inhibit the naturally occurring enzyme activity.

Native: refers to a gene that is present in the genome of an untransformed insect cell.

Naturally occurring: the term "naturally occurring" is used to describe an object that can be found in nature as distinct from being artificially produced by man. For example, a protein or nucleotide sequence present in an organism (including a virus), which can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory, is naturally occurring.

Nucleic acid: the term "nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides which have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g. degenerate codon substitutions) and complementary sequences and as well as the sequence



explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.*, *Nucleic Acid Res.* 19: 5081 (1991); Ohtsuka *et al.*, *J. Biol. Chem.* 260: 2605-2608 (1985); Rossolini *et al.*, *Mol. Cell. Probes* 8: 91-98 (1994)). The terms "nucleic acid" or "nucleic acid sequence" may also be used interchangeably with gene, cDNA, and mRNA encoded by a gene.

"ORF" means open reading frame.

Purified: the term "purified," when applied to a nucleic acid or protein, denotes that the nucleic acid or protein is essentially free of other cellular components with which it is associated in the natural state. It is preferably in a homogeneous state although it can be in either a dry or aqueous solution. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. A protein which is the predominant species present in a preparation is substantially purified. The term "purified" denotes that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. Particularly, it means that the nucleic acid or protein is at least about 50% pure, more preferably at least about 85% pure, and most preferably at least about 99% pure.

Two nucleic acids are "recombined" when sequences from each of the two nucleic acids are combined in a progeny nucleic acid. Two sequences are "directly" recombined when both of the nucleic acids are substrates for recombination. Two sequences are "indirectly recombined" when the sequences are recombined using an intermediate such as a cross-over oligonucleotide. For indirect recombination, no more than one of the sequences is an actual substrate for recombination, and in some cases, neither sequence is a substrate for recombination.

"Regulatory elements" refer to sequences involved in controlling the expression of a nucleotide sequence. Regulatory elements comprise a promoter operatively linked to the nucleotide sequence of interest and termination signals. They also typically encompass sequences required for proper translation of the nucleotide sequence.

Significant Increase: an increase in enzymatic activity that is larger than the margin of error inherent in the measurement technique, preferably an increase by about 2-fold or greater of the activity of the wild-type enzyme in the presence of the inhibitor, more preferably an increase by about 5-fold or greater, and most preferably an increase by about 10-fold or greater.

Substantially identical: the phrase "substantially identical," in the context of two nucleic acid or protein sequences, refers to two or more sequences or subsequences that have at least 60%, preferably 80%, more preferably 90, even more preferably 95%, and most preferably at least 99% nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection. Preferably, the substantial identity exists over a region of the sequences that is at least about 50 residues in length, more preferably over a region of at least about 100 residues, and most preferably the sequences are substantially identical over at least about 150 residues. In an especially preferred embodiment, the sequences are substantially identical over the entire length of the coding regions. Furthermore, substantially identical nucleic acid or protein sequences perform substantially the same function.

For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2: 482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48: 443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85: 2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (*see generally*, Ausubel *et al.*, *infra*).

One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul *et al.*, *J. Mol. Biol.* 215: 403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information on the world wide web at [ncbi.nlm.nih.gov/](http://ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, 1990). These initial neighborhood word hits act as seeds for initiating searches to find

longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always  $> 0$ ) and N (penalty score for mismatching residues; always  $< 0$ ). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when the cumulative alignment score falls off by the quantity X from its maximum achieved value, the cumulative score goes to zero or below due to the accumulation of one or more negative-scoring residue alignments, or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, a cutoff of 100,  $M=5$ ,  $N=-4$ , and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (*see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89: 10915 (1989)*).

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g., Karlin & Altschul, Proc. Natl. Acad. Sci. USA 90: 5873-5787 (1993)*). One measure of similarity provided by the BLAST algorithm is the smallest sum probability ( $P(N)$ ), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a test nucleic acid sequence is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid sequence to the reference nucleic acid sequence is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions. The phrase "hybridizing specifically to" refers to the binding, duplexing, or hybridizing of a molecule only to a particular nucleotide sequence under stringent conditions when that sequence is present in a complex mixture (*e.g., total cellular*) DNA or RNA. "Bind(s) substantially" refers to complementary hybridization between a probe nucleic acid and a target nucleic acid and embraces minor mismatches that can be accommodated by reducing the stringency of the hybridization media to achieve the desired detection of the target nucleic acid sequence.

"Stringent hybridization conditions" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization experiments such as Southern and Northern hybridizations are sequence dependent, and are different under different environmental parameters. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen (1993) *Laboratory Techniques in Biochemistry and Molecular Biology-Hybridization with Nucleic Acid Probes* part I chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays" Elsevier, New York. Generally, highly stringent hybridization and wash conditions are selected to be about 5°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. Typically, under "stringent conditions" a probe will hybridize to its target subsequence, but to no other sequences.

The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Very stringent conditions are selected to be equal to the  $T_m$  for a particular probe. An example of stringent hybridization conditions for hybridization of complementary nucleic acids which have more than 100 complementary residues on a filter in a Southern or northern blot is 50% formamide with 1 mg of heparin at 42°C, with the hybridization being carried out overnight. An example of highly stringent wash conditions is 0.1 M NaCl at 72°C for about 15 minutes. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (*see*, Sambrook, *infra*, for a description of SSC buffer). Often, a high stringency wash is preceded by a low stringency wash to remove background probe signal. An example medium stringency wash for a duplex of, e.g., more than 100 nucleotides, is 1x SSC at 45°C for 15 minutes. An example low stringency wash for a duplex of, e.g., more than 100 nucleotides, is 4-6x SSC at 40°C for 15 minutes. For short probes (*e.g.*, about 10 to 50 nucleotides), stringent conditions typically involve salt concentrations of less than about 1.0 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3, and the temperature is typically at least about 30°C. Stringent conditions can also be achieved with the addition of destabilizing agents such as formamide. In general, a signal to noise ratio of 2x (or higher) than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization. Nucleic acids that do not hybridize to each other under stringent conditions are still substantially identical if the proteins that they encode are substantially identical. This occurs, e.g., when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code.

The following are examples of sets of hybridization/wash conditions that may be used to clone homologous nucleotide sequences that are substantially identical to reference nucleotide sequences of the present invention: a reference nucleotide sequence preferably hybridizes to the reference nucleotide sequence in 7% sodium dodecyl sulfate (SDS), 0.5 M  $\text{NaPO}_4$ , 1 mM EDTA at 50°C with washing in 2X SSC, 0.1% SDS at 50°C, more desirably in 7% sodium dodecyl sulfate (SDS), 0.5 M  $\text{NaPO}_4$ , 1 mM EDTA at 50°C with washing in 1X SSC, 0.1% SDS at 50°C, more desirably still in 7% sodium dodecyl sulfate (SDS), 0.5 M  $\text{NaPO}_4$ , 1 mM EDTA at 50°C with washing in 0.5X SSC, 0.1% SDS at 50°C, preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M  $\text{NaPO}_4$ , 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 50°C, more preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M  $\text{NaPO}_4$ , 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 65°C.

A further indication that two nucleic acid sequences or proteins are substantially identical is that the protein encoded by the first nucleic acid is immunologically cross reactive with, or specifically binds to, the protein encoded by the second nucleic acid. Thus, a protein is typically substantially identical to a second protein, for example, where the two proteins differ only by conservative substitutions.

The phrase "specifically (or selectively) binds to an antibody," or "specifically (or selectively) immunoreactive with," when referring to a protein or peptide, refers to a binding reaction which is determinative of the presence of the protein in the presence of a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein and do not bind in a significant amount to other proteins present in the sample. Specific binding to an antibody under such conditions may require an antibody that is selected for its specificity for a particular protein. For example, antibodies raised to the protein with the amino acid sequence encoded by any of the nucleic acid sequences of the invention can be selected to obtain antibodies specifically immunoreactive with that protein and not with other proteins except for polymorphic variants. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays, Western blots, or immunohistochemistry are routinely used to select monoclonal antibodies specifically immunoreactive with a protein. See Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, New York ("Harlow and Lane"), for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity. Typically a specific or selective reaction will be

at least twice background signal or noise and more typically more than 10 to 100 times background.

A "subsequence" refers to a sequence of nucleic acids or amino acids that comprise a part of a longer sequence of nucleic acids or amino acids (e.g., protein) respectively.

"Synthetic" refers to a nucleotide sequence comprising structural characters that are not present in the natural sequence. For example, an artificial sequence that resembles more closely the G+C content and the normal codon distribution of dicot and/or monocot genes is said to be synthetic.

Substrate: a substrate is the molecule that an enzyme naturally recognizes and converts to a product in the biochemical pathway in which the enzyme naturally carries out its function, or is a modified version of the molecule, which is also recognized by the enzyme and is converted by the enzyme to a product in an enzymatic reaction similar to the naturally-occurring reaction.

Target gene: A "target gene" is any gene in an insect cell. For example, a target gene is a gene of known function or is a gene whose function is unknown, but whose total or partial nucleotide sequence is known. Alternatively, the function of a target gene and its nucleotide sequence are both unknown. A target gene is a native gene of the insect cell or is a heterologous gene that had previously been introduced into the insect cell or a parent cell of said insect cell, for example by genetic transformation. A heterologous target gene is stably integrated in the genome of the insect cell or is present in the insect cell as an extrachromosomal molecule, e.g. as an autonomously replicating extrachromosomal molecule.

Transformation: a process for introducing heterologous DNA into a cell, tissue, or insect. Transformed cells, tissues, or insects are understood to encompass not only the end product of a transformation process, but also transgenic progeny thereof.

"Transformed," "transgenic," and "recombinant" refer to a host organism such as a bacterium or a plant into which a heterologous nucleic acid molecule has been introduced. The nucleic acid molecule can be stably integrated into the genome of the host or the nucleic acid molecule can also be present as an extrachromosomal molecule. Such an extrachromosomal molecule can be auto-replicating. Transformed cells, tissues, or plants are understood to encompass not only the end product of a transformation process, but also transgenic progeny thereof. A "non-transformed," "non-transgenic," or "non-recombinant" host refers to a wild-type organism, e.g., a bacterium or plant, which does not contain the

heterologous nucleic acid molecule.

Viability: "viability" as used herein refers to a fitness parameter of an insect. Insects are assayed for their homozygous performance of *Drosophila* larval development, indicating which proteins are indispensable to maintain larval life in *Drosophila*.

## DETAILED DESCRIPTION OF THE INVENTION

### I. Identification Of Essential *Drosophila melanogaster* Nucleotide Sequences Using Transposable Element Insertion Mutagenesis

As shown in the examples below, the identification of novel nucleotide sequences, as well as the essentiality of the nucleotide sequences for normal insect viability, have been demonstrated in *Drosophila* using P-element transposable insertion mutagenesis. Having established the essentiality of the function of the encoded proteins in *Drosophila* and having identified the nucleotide sequences encoding these essential proteins, the inventors thereby provide an important and sought-after tool for new insecticide development.

A lethal phenotype caused by insertion of a P-element indicates that the affected nucleotide sequence codes for an essential protein in the insect. The characterization of the insertion site using flanking sequence DNA is needed to associate an individual larval lethal line with specific nucleotide sequences. Genomic DNA adjacent to the 5' and/or 3' end of the P-element from the insertion line is generated using inverse PCR.

### II. Determining The Complete Coding Sequences Of The Essential *Drosophila* Nucleotide Sequences

The essential *Drosophila* nucleotide sequences are identified by isolating nucleotide sequences flanking the P-element insertion and aligning that sequence with genomic *Drosophila* sequence obtained from the Celera *Drosophila* database. The protein prediction for each genomic region is obtained by use of an exon algorithm program such as GeneMark. All exon algorithm programs currently used for prediction of proteins are susceptible to inaccuracies, including incomplete predictions of coding sequences, missing alternative splice variants, combining of nearby exons of adjacent genes, and mistranslation at intron-exon borders. The prediction of a complete coding sequence can be confirmed by several methods including polymerase chain reaction (PCR) amplification using the 5' and 3' sequence to verify the message, reverse transcription PCR (rtPCR) using an oligonucleotide internal

sequence to identify the 5' and/or 3' end, and screening of cDNA libraries from insect tissues with probes made from a particular sequence to isolate a true full-length clone. To confirm that the message size is accurate, a Northern blot can be hybridized with a probe from the nucleotide sequence. In addition, matches to the *Drosophila* EST database helps to confirm existence of message and gives information about the temporal and spatial pattern of expression. Mutation-causing P elements are known to preferentially cluster in the 5' region of affected genes (Spradling *et al.*, *Proc. Natl. Acad. Sci. USA* 92: 10824-10830 (1995)), a tendency that increases the chance of recovering overlaps between short flanking sequences and 5' ESTs. The present invention therefore provides a number of essential nucleotide sequences as well as the amino acid sequences encoded thereby. cDNA clone sequences are set forth in odd numbered SEQ ID NOs:1-73. The corresponding encoded amino acid sequences are set forth in even numbered SEQ ID NOs:2-74.

The isolated gene sequences disclosed herein may be manipulated according to standard genetic engineering techniques to suit any desired purpose. For example, an entire *Drosophila* gene sequence or portions thereof may be used as a probe capable of specifically hybridizing to coding sequences and messenger RNAs. To achieve specific hybridization under a variety of conditions, such probes include, e.g. sequences that are unique among insect nucleotide sequences for a particular protein of interest and are at least 10 nucleotides in length, preferably at least 20 nucleotides in length, and most preferably at least 50 nucleotides in length. Such probes are used to amplify and analyze related nucleotide sequences from a chosen organism via PCR. This technique is useful to isolate additional insect nucleotide sequences from a desired organism or as a diagnostic assay to determine the presence of particular nucleotide sequences in an organism. This technique also is used to detect the presence of altered nucleotide sequences associated with a particular condition of interest such as insecticide tolerance, poor health, etc.

Gene-specific hybridization probes also are used to quantify levels of a particular gene mRNA in an insect using standard techniques such as Northern blot analysis. This technique is useful as a diagnostic assay to detect altered levels of gene expression that are associated with particular conditions such as enhanced tolerance to insecticides that target a particular gene.



### III. Recombinant Production Of Protein And Uses Thereof

For recombinant production of a protein of the invention in a host organism, a nucleotide sequence encoding the protein is inserted into an expression cassette designed for the chosen host and introduced into the host where it is recombinantly produced. The choice of the specific regulatory sequences such as promoter, signal sequence, 5' and 3' untranslated sequence, and enhancer appropriate for the chosen host is within the level of the skill of the routineer in the art. The resultant molecule, containing the individual elements linking in the proper reading frame, is inserted into a vector capable of being transformed into the host cell. Suitable expression vectors and methods for recombinant production of proteins are well known for host organisms such as *E. coli*, yeast, and insect cells (see, e.g., Lucknow and Summers, *Bio/Technol.* 6:47 (1988)). Additional suitable expression vectors are baculovirus expression vectors, e.g., those derived from the genome of *Autographica californica* nuclear polyhedrosis virus (AcMNPV). A preferred baculovirus/insect system is PVL1392(3) used to transfect *Spodoptera frugiperda* SF9 cells (ATCC) in the presence of linear *Autographica californica* baculovirus DNA (Phramingen, San Diego, CA). The resulting virus is used to infect HighFive *Tricoplusia ni* cells (Invitrogen, La Jolla, CA).

Recombinantly produced proteins are isolated and purified using a variety of standard techniques. The actual techniques used vary depending upon the host organism used, whether the protein is designed for secretion, and other such factors. Such techniques are well known to the skilled artisan (see, e.g. chapter 16 of Ausubel, F. *et al.*, "Current Protocols in Molecular Biology", pub. by John Wiley & Sons, Inc. (1994).

### IV. Assays For Characterizing The Proteins

Recombinantly produced proteins are useful for a variety of purposes. For example, they can be used in *in vitro* assays to screen known insecticidal chemicals whose target has not been identified to determine if they inhibit protein activity. Such *in vitro* assays may also be used as more general screens to identify chemicals that inhibit such protein activity and that are therefore novel insecticide candidates. Recombinantly produced proteins may also be used to elucidate the complex structure of these molecules and to further characterize their association with known inhibitors in order to rationally design new inhibitory insecticides. Alternatively, the recombinant protein can be used to isolate antibodies or peptides that modulate the activity and are useful in transgenic solutions.

V. *In vivo* Inhibitor Assay: Discovery of Small Molecule Ligands That Interact with Proteins Of Unknown Function.

Having identified a protein as a potential insecticide target based on its essentiality for insect larval viability, a next step is to develop an assay that allows screening large numbers of chemicals to determine which ones interact with the protein. Although it is straightforward to develop assays for proteins of known function, developing assays with proteins of unknown functions can be more difficult.

To address this issue, novel technologies are used that can detect interactions between a protein and a ligand without knowing the biological function of the protein. A short description of three methods is presented, including fluorescence correlation spectroscopy, surface-enhanced laser desorption/ionization, and biacore technologies. In addition to those described here, there are additional methods that are currently being developed that are also amenable to automated, large-scale screening.

Fluorescence Correlation Spectroscopy (FCS) theory was developed in 1972 but it is only in recent years that the technology to perform FCS became available (Madge et al. (1972) *Phys. Rev. Lett.*, 29: 705-708; Maiti et al. (1997) *Proc. Natl. Acad. Sci. USA*, 94: 11753-11757). FCS measures the average diffusion rate of a fluorescent molecule within a small sample volume. The sample size can be as low as  $10^3$  fluorescent molecules and the sample volume as low as the cytoplasm of a single bacterium. The diffusion rate is a function of the mass of the molecule and decreases as the mass increases. FCS can therefore be applied to protein-ligand interaction analysis by measuring the change in mass and therefore in diffusion rate of a molecule upon binding. In a typical experiment, the target to be analyzed is expressed as a recombinant protein with a sequence tag, such as a poly-histidine sequence, inserted at the N- or C-terminus. The expression takes place in *E. coli*, yeast or insect cells. The protein is purified by chromatography. For example, the poly-histidine tag can be used to bind the expressed protein to a metal chelate column such as Ni<sup>2+</sup> chelated on iminodiacetic acid agarose. The protein is then labeled with a fluorescent tag such as carboxytetramethylrhodamine or BODIPY® (Molecular Probes, Eugene, OR). The protein is then exposed in solution to the potential ligand, and its diffusion rate is determined by FCS using instrumentation available from Carl Zeiss, Inc. (Thornwood, NY). Ligand binding is determined by changes in the diffusion rate of the protein.

Surface-Enhanced Laser Desorption/Ionization (SELDI) was invented by Hutchens and Yip during the late 1980's (Hutchens and Yip (1993) *Rapid Commun. Mass Spectrom.* 7: 576-

580). When coupled to a time-of-flight mass spectrometer (TOF), SELDI provides means to rapidly analyze molecules retained on a chip. It can be applied to ligand-protein interaction analysis by covalently binding the target protein on the chip and analyze by MS the small molecules that bind to this protein (Worrall et al. (1998) *Anal. Biochem.* 70: 750-756). In a typical experiment, the target to be analyzed is expressed as described for FCS. The purified protein is then used in the assay without further preparation. It is bound to the SELDI chip either by utilizing the poly-histidine tag or by other interaction such as ion exchange or hydrophobic interaction. The chip thus prepared is then exposed to the potential ligand via, for example, a delivery system able to pipet the ligands in a sequential manner (autosampler). The chip is then submitted to washes of increasing stringency, for example a series of washes with buffer solutions containing an increasing ionic strength. After each wash, the bound material is analyzed by submitting the chip to SELDI-TOF. Ligands that specifically bind the target will be identified by the stringency of the wash needed to elute them.

Biacore relies on changes in the refractive index at the surface layer upon binding of a ligand to a protein immobilized on the layer. In this system, a collection of small ligands is injected sequentially in a 2-5 microlitre cell with the immobilized protein. Binding is detected by surface plasmon resonance (SPR) by recording laser light refracting from the surface. In general, the refractive index change for a given change of mass concentration at the surface layer is practically the same for all proteins and peptides, allowing a single method to be applicable for any protein (Liedberg et al. (1983) *Sensors Actuators* 4: 299-304; Malmquist (1993) *Nature* 361: 186-187). In a typical experiment, the target to be analyzed is expressed as described for FCS. The purified protein is then used in the assay without further preparation. It is bound to the Biacore chip either by utilizing the poly-histidine tag or by other interaction such as ion exchange or hydrophobic interaction. The chip thus prepared is then exposed to the potential ligand via the delivery system incorporated in the instruments sold by Biacore (Uppsala, Sweden) to pipet the ligands in a sequential manner (autosampler). The SPR signal on the chip is recorded and changes in the refractive index indicate an interaction between the immobilized target and the ligand. Analysis of the signal kinetics on rate and off rate allows the discrimination between non-specific and specific interaction.

The compounds that are active in the methods disclosed herein may be used to combat agricultural pests such as aphids, locusts, spider mites, and boll weavils as well as such insect pests which attack stored grains and against immature stages of insects living on plant tissue.

The compounds are also useful as a nematocide for the control of agriculturally important soil nematodes and plant parasites.

#### VI. Production of peptides

Phage particles displaying diverse peptide libraries permits rapid library construction, affinity selection, amplification and selection of ligands directed against an essential protein (H.B. Lowman, *Annu. Rev. Biophys. Biomol. Struct.* 26, 401-424 (1997)). Structural analysis of these selectants can provide new information about ligand-target molecule interactions and then in the process also provide a novel molecule that can enable the development of new insecticides based upon these peptides as leads.

The invention will be further described by reference to the following detailed examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified.

### EXAMPLES

Standard recombinant DNA and molecular cloning techniques used here are well known in the art and are described by Sambrook, *et al.*, *Molecular Cloning*, eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1989) and by T.J. Silhavy, M.L. Berman, and L.W. Enquist, *Experiments with Gene Fusions*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1984) and by Ausubel, F.M. *et al.*, *Current Protocols in Molecular Biology*, pub. by Greene Publishing Assoc. and Wiley-Interscience (1987). Well known *Drosophila* molecular genetics techniques can be found, for example, in Robert, D.B., *Drosophila, A Practical Approach* (IRL Press, Washington, DC, 1986).

#### Example 1: Identification Of Larval Lethal Lines

Essential nucleotide sequences are identified through the isolation of lethal mutants defective in larval development. The genetic scheme for mobilization of P-lacW is as performed in Deak *et. al*, *Genetics* 147: 1697-1722 (1997). Additional larval lethal lines are identified and disclosed in Braun, A., B. Lemaitre, *et al.*, *Genetics* 147: 623-634 (1997); Galloni, M. and B. A. Edgar, *Development* 126: 2365-2375 (1999); Gateff, E., *Int. J. Dev. Biol.* 38(4): 565-590 (1994); Mechler, B. M. J. Biosci., *Bangalore* 19(5): 537-556 (1994);

Roch, F., F. Serras, *et al.*, *Mol. Gen. Genet.* 257: 103-112 (1998); Russell, M. A., L. Ostafichuk, *et al.*, *Genome* 41: 7-13 (1998); and in Torok, T., G. Tick, *et al. Genetics* 135: 71-80 (1993). Furthermore, the BDGP gene disruption project of single P-element insertions reveals larval lethal lines mutating 25% of vital *Drosophila* genes Spradling, A. C., D. Stern, *et al.*, *Genetics* 153: 135-177 (1999).

Males carrying the transposase source P( $\Delta$ 2-3) are crossed en masse to yellow white females homozygous for a P-lacW insertion on the X chromosome. Males carrying the PlacW insertion on the X and  $\Delta$ 2-3 on the third chromosome are collected from this cross. The F0 "jumpstart" males are crossed in groups of 10-15 to 20-25 females of w spl; Sb/TM3, Ser genotype. Male F1 progeny with pigmented eyes indicate that the P-lacW has jumped to an autosome. An average of 10-15 males from each F0 cross lacking  $\Delta$ 2-3 are crossed individually to y w; DTS-4/TM3, Sb Ser females, that all third chromosomal insertions result in balanced F2 stocks. Insertions on other autosomes yield white-eyed flies in the F2 generation and are eliminated. The balanced third chromosome insertions are tested for lethality in the next generation by placing four to six pairs of y w; P-lacW/TM3, Sb Ser flies in a vial and examining their progeny for the presence of homozygous P-lacW flies. To analyze the lethal phase, the TM3, Sb Ser balancer is replaced by the TM6C, TB Sb chromosome. In such a genetic background, homozygous mutants can be identified by their wild-type body-length. An average of 10-15 pairs of flies are placed in vials supplemented with yeast paste, and the eggs are collected from each line for 1 day. The development of 50-100 progeny is monitored, and the presence of homozygotes are recorded in all developmental stages. Lethal phase is assigned to a developmental stage in which homozygote animals last appear. Larval lethal lines are identified and maintained.

#### Example 2: Sequence Determination

Inverse PCR: To determine the flanking sequence of the larval lethal lines, the "Inverse PCR and Cycle Sequencing Protocol for Recovery of Sequences Flanking PZ, PlacW, and PEP elements" of E. Jay Rehm, Berkeley *Drosophila* Genome Project on the world wide web at [fruitfly.org/methods/](http://fruitfly.org/methods/) is used with slight modifications. These modifications include the following: genomic DNA is obtained from 10 flies, rather than 30 flies, with adjustments for final concentrations; all DNA precipitations are performed using glycogen; for some

Digest, End, Temperature	Forward PCR Primer	Reverse PCR Primer
H5h	Plac4	Plac1
H3h	Pry2	Pry1
H3l	Pry4	Plw3-1
M5h	Plac4	Plac1
M3h	Pry2	Pry1
M3l	Pry4	Plw3-1
S5h	Plac4	Plac1
S3h	Pry2	Pry1
S3l	Pry4	Plw3-1

PCR Primer Sequences (5' to 3'):

Plac4 (27)	- act gtg cgt tag gtc ctg ttc att gtt	SEQ ID NO:75
Plac1 (24)	- cac cca agg ctc tgc tcc cac aat	SEQ ID NO:76
Pry4 (23)	- caa tca tat cgc tgt ctc act ca	SEQ ID NO:77
Pry1 (26)	- cct tag cat gtc cgt ggg gtt tga at	SEQ ID NO:78
Pry2 (28)	- ctt gcc gac ggg acc acc tta tgt tat t	SEQ ID NO:79
Plw3-1 (19)	- tgt cgg cgt cat caa ctc c	SEQ ID NO:80
Pwht1 (19)	- gta acg cta atc act ccg aac agg tca ca	SEQ ID NO:81

Enzymatic Clean-Up for Sequencing: To 40  $\mu$ l PCR reaction, add 4  $\mu$ l of enzyme mix. Incubate at 37°C for 1 hour. Inactivate at 70°C for 10 minutes. (Enzyme Mix consists of 2.5U/ $\mu$ l Exonuclease I (Amersham E700732), 0.5U/ $\mu$ l Shrimp Alkaline Phosphatase (Amersham E70183), 1X Amplitaq PCR buffer, add dH<sub>2</sub>O to final volume.)

Example 3: Sequence Analysis

Sequence of the flanking sequence generated by inverse PCR is performed on an ABI 3700 sequencer (Perkin Elmer) using BIG DYE sequencing reaction.

Primer sets for sequencing are as shown in the table below:

Digest, End, Temperature	Forward Primer	Reverse Primer
H5h	Splac2	Sp1
H3h	Pry2	Sp5
H3l	Spep1	Sp5
M5h	Splac2	Sp1
M3h	Pry2	Sp5
M3l	Spep1	Sp5
S5h	Splac2	Sp1
S3h	Pry2	Sp6
S3l	Spep1	Sp6

The following primer sets are designed to sequence both ends of PCR products recovered from PlacW and PZ strains:

Splac2 and Sp1 - for use with the Plac4/Plac1 5' PCR primer combination with either PZ or PlacW P-elements; allows sequencing of both ends of the PCR fragment.

Spep1 and Sp3 - for use with the Pry4/Pry1 3' PCR primer combination with PZ P-elements; allows sequencing of both ends of the PCR fragment.

Spep1 and Sp6 - for use with the Pry4/Plw3-1 3' PCR primer combination with PlacW P-elements where Sau3a digestion is performed; allows sequencing of both ends of the PCR fragment.

Spep1 and Sp5 - for use with the Pry4/Plw3-1 3' PCR primer combination where HinP1 digestion is performed; allows sequencing of both ends of the PCR fragment.

Pry1 and Pry2 - for use with the Pry1/Pry2 3' PCR primer combination; allows sequencing of both ends of the PCR fragment.

The PCR products recovered from PEP strains are sequenced with the following primers: Sp1- for use with the Pwht1/Plac1 5' PCR primer combination with the PEP element; Spep1- for use with the Pry4/Pry1 3' PCR primer combination with the PEP element; Pry1 and Pry2 for use with the Pry1/Pry2 3' PCR primer combination with the PEP element.

## Primer Sequences (5' to 3'):

Splac2 (25)	- gaa ttc act ggc cgt cgt ttt aca a	SEQ ID NO:82
Sp1 (22)	- aca caa cct ttc ctc tca aca a	SEQ ID NO:83
Sp3 (24)	- gag tac gca aag ctt taa cta tgt	SEQ ID NO:84
Sp6 (23)	- tga cca cat cca aac atc ctc tt	SEQ ID NO:85
Sp5 (25)	- gca tca caa aaa tcg acg ctc aag t	SEQ ID NO:86
Spep1 (19)	- gac act cag aat act att c	SEQ ID NO:87

## Melting temperatures of sequencing primers:

Splac2-	60.1°C
Sp1-	50.6°C
Sp3-	49.3°C
Sp6-	54.9°C
Sp5 -	60.3°C
Spep1-	44.8°C

## Example 4: Secondary Confirmation of Lethality

The lethality of the chromosome carrying the P-element insertion is demonstrated genetically as described in Example 1. The essential *Drosophila* nucleotide sequences are identified by isolating nucleotide sequences flanking the P-element insertion and aligning those sequences with genomic *Drosophila* sequence obtained from the Celera *Drosophila* database. However, in some instances, a second site mutation exists on the chromosome that is responsible for the lethality. In other instances, the location of the flanking sequence is such that determination of which gene(s) are affected by the P-element insertion is rendered difficult or impossible. Thus, to provide secondary confirmation that the gene indicated is essential, there are many methods that one skilled in the art can use, e.g., rescue of the lethality using transformation technology, perturbation of the gene in a targeted manner, or failure to complement a deficiency.

To provide secondary confirmation, larval lethal lines are crossed to a line containing a deficiency spanning the region of the insert. This creates a hemizygous condition in that particular region and reveals the recessive phenotype of the P-element. Complementation with deficiencies that unequivocally remove the P-element insertion site is taken as proof that the P-element does not cause the associated phenotype. Failure to complement indicates that



the strain is verified. This method is as performed in Spradling, A. C., D. Stern, *et al.*, *Genetics* 153: 135-177 (1999). While lines with secondary mutations closely linked to the P insertion might be erroneously verified by this procedure, further molecular and genetic analyses suggest that the frequency of such errors is small. RNA interference, described in Fire, A., S. Xu, *et al.*, *Nature* 391, 806-811 (1998) and Kennerdell, J.R. and Carthew, R.W., *Cell* 95, 1017-1026 (1998), is used as a method to target a gene of interest and demonstrate that the perturbation of the identified gene produces a lethal phenotype.

#### Example 5: Isolation Of Full Length cDNA

A cDNA screen is performed using a *Drosophila melanogaster* cDNA library probed with a portion of each nucleotide sequence disclosed in the Sequence Listing. Positive colonies are selected, a subset sequenced, and a clone corresponding to the full-length cDNA is recovered. Alternatively, primers from the predicted 5' and 3' end are used in polymerase chain reaction with either a *Drosophila* cDNA library or first strand cDNAs obtained by reverse transcription of *Drosophila* mRNAs as template to amplify a fragment representing the full-length clone.

#### Example 6: Expression Of Recombinant Protein In Insect Cells

Baculovirus vectors, which are derived from the genome of AcNPV virus, are designed to provide high levels of expression of cDNA in the SF9 line of insect cells (ATCC CRL# 1711). Recombinant baculovirus expressing the cDNA of the present invention is produced by the following standard methods (InVitrogen MaxBac Manual): cDNA constructs are ligated into the polyhedrin gene in a variety of baculovirus transfer vectors, including the pAC360 and the BleBac vector (InVitrogen). Recombinant baculoviruses are generated by homologous recombination following co-transfection of the baculovirus transfer vector and linearized AcNPV genomic DNA (Kitts, P.A., *Nucleic Acid. Res.* 18: 5667 (1990)) into SF9 cells. Recombinant pAC360 viruses are identified by the absence of inclusion bodies in infected cells and recombinant pBlueBac viruses are identified on the basis of B-galactosidase expression (Summers, M.D. and Smith, G.E., Texas Agriculture Exp. Station Bulletin No. 1555). Following plaque purification, the *Drosophila* cDNA expression is measured.

The cDNA encoding the entire open reading frame for the *Drosophila* cDNA is inserted into the BamHI site of pBlueBacII. Constructs in the positive orientation, which are identified by sequence analysis, are used to transfect SF9 cells in the presence of linear AcNPV wild type DNA. Authentic, active *Drosophila* cDNA is found in the cytoplasm of infected cells. Active *Drosophila* cDNA is extracted from infected cells by hypotonic or detergent lysis.

#### Example 7: Expression Of Recombinant Protein In *E. coli*

A cDNA clone of the present invention is subcloned into an appropriate expression vector and transformed into *E. coli* using the manufacturer's conditions. Specific examples include plasmids such as pBluescript (Stratagene, La Jolla, CA), pFLAG (International Biotechnologies, Inc., New Haven, CT), and pTrcHis (Invitrogen, La Jolla, CA). *E. coli* is cultured, and expression of the recombinant protein is confirmed. Recombinant protein is then isolated using standard techniques.

#### Example 8: *In vitro* Binding Assays

Recombinant protein is obtained, for example according to Example 6 or Example 7. The protein is immobilized on chips appropriate for ligand binding assays. The protein immobilized on the chip is exposed to sample compound in solution according to methods well known in the art. While the sample compound is in contact with the immobilized protein measurements capable of detecting protein-ligand interactions are conducted. Examples of such measurements are SEDLI, biacore and FCS, described above. Compounds found to bind the protein are readily discovered in this fashion and are subjected to further characterization.

The above disclosed embodiments are illustrative. This disclosure of the invention will place one skilled in the art in possession of many variations of the invention. All such obvious and foreseeable variations are intended to be encompassed by the appended claims.

What is claimed is:

1. A method for identifying a compound that inhibits the activity of a protein essential for *Drosophila* larval viability, comprising:
  - (a) expressing in a recombinant host a DNA molecule comprising
    - (i) a nucleotide sequence selected from the group consisting of the odd numbered SEQ ID NOs:1-73, or
    - (ii) a nucleotide sequence encoding an amino acid sequence selected from the group consisting of the even numbered SEQ ID NOs:2-74,to produce a protein essential for *Drosophila* larval viability;
  - (b) testing compounds suspected of having the ability to inhibit the activity of the protein expressed in (a); and
  - (c) identifying a compound tested in (b) that inhibits the activity of the protein.
2. A method for killing or inhibiting the growth or viability of an insect, comprising applying to the insect a compound identified according to the method of claim 1.
3. A method for identifying a compound that interacts with a protein essential for *Drosophila* larval viability, comprising:
  - (a) expressing in a recombinant host a DNA molecule comprising
    - (i) a nucleotide sequence selected from the group consisting of the odd numbered SEQ ID NOs:1-73, or
    - (ii) a nucleotide sequence encoding an amino acid sequence selected from the group consisting of the even numbered SEQ ID NOs:2-74,to produce a protein essential for *Drosophila* larval viability;
  - (b) testing compounds suspected of having the ability to interact with the protein expressed in (a); and
  - (c) identifying a compound tested in (b) that interacts with the protein.
4. A method for killing or inhibiting the growth or viability of an insect, comprising applying to the insect a compound identified according to the method of claim 3.

5. A method for killing or inhibiting the growth or viability of an insect, comprising inhibiting expression in said insect of a protein having at least 60% sequence identity to an amino acid sequence selected from the group consisting of the even numbered SEQ ID NOs:2-74.

6. The method of claim 5, wherein expression of said protein is inhibited by disruption in said insect of a nucleotide sequence having at least 60% sequence identity to a nucleotide sequence selected from the group consisting of the odd numbered SEQ ID NOs:1-73.

7. The method of claim 6, wherein said nucleotide sequence is disrupted by RNA interference.

## SEQUENCE LISTING

<110> Stam, Lynn  
 Bachmann, Jane  
 Broadus, Julie  
 Kamdar, Kim

<120> NUCLEIC ACID SEQUENCES FROM DROSOPHILA MELANOGASTER THAT ENCODE  
 PROTEINS ESSENTIAL FOR LARVAL VIABILITY AND USES THEREOF

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<213> Drosophila melanogaster

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 tgcactact tccgatgtcg gggggccac atcacgagtc acctgcgac caagaagcac 960

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&lt;210&gt; 10

&lt;211&gt; 735

&lt;212&gt; PRT

<213> *Drosophila melanogaster*

&lt;400&gt; 10

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          35           40           45
Lys Ala Ser Glu Lys Ser Gln Lys Phe Thr Lys Lys Lys Pro Asn Tyr

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Ser Val Phe Ser Ser Ser Ser Ser Ser Ser Gly Arg Ser Phe Gly 115 120 125		
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Ala Glu Asn Glu Thr Leu Ala Val Ala Ala Ala Ala Thr Thr Thr 145 150 155 160		
Asn Ala Gly Arg Phe Ile Thr Ala Asp Leu Ile Lys Thr Val Asn Ser 165 170 175		
Asp Lys Gln Arg Asp Arg Val Ala Lys Gly His Arg Asp Ala Lys Asn 180 185 190		
Pro Leu Asp Ala Thr Lys His Leu Arg Leu Ser Asp Cys Leu Arg Thr 195 200 205		
Val Gln Lys Leu Ala Ile Glu Leu Glu Ser Ala Asp Ala Gly Ser Asp 210 215 220		
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Tyr Asp Thr Phe Arg Val Ile Asp Ala Tyr Phe Ala Ala Cys Val Asn 260 265 270		
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Gly Ser Tyr Gly Ile Gln Leu Tyr Ala Cys Leu His Cys Ile Tyr Phe 290 295 300		
Gly Cys Arg Gly Ala His Ile Thr Ser His Leu Arg Ser Lys Lys His 305 310 315 320		
Asn Val Ala Leu Glu Leu Ser His Gly Thr Leu Tyr Cys Tyr Ala Cys 325 330 335		
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Arg Lys Leu Glu Ala Lys Asp Leu Gln Lys Ser Ile Gly Trp Val Pro 355 360 365		
Trp Val Pro Thr Thr Lys Glu Thr Asn Leu Leu Leu Ala Asn Ala Arg 370 375 380		



Arg Arg Leu Val Arg Pro Asn Gln Thr Ile Gly Leu Arg Gly Leu Leu  
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 405 410 415  
 His Thr Pro Leu Leu Ser Asp Tyr Phe Met Ser Asp Arg His Asp Cys  
 420 425 430  
 Gly Ser Lys Ser Ser His Lys Cys Leu Val Cys Glu Val Ser Arg Leu  
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 Arg His Cys Val Lys Ala Lys Ala Glu His Glu Ser Lys Ser Asn Ser  
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 515 520 525  
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 His Gly Gly Val Thr Pro Lys Thr Leu Ile Asp Cys Leu Glu Arg Tyr  
 580 585 590  
 Thr Arg Ala Glu His Leu Gly Ser Ala Ala Lys Ile Lys Cys Ser Thr  
 595 600 605  
 Cys Lys Ser Tyr Gln Glu Ser Thr Lys Gln Phe Ser Leu Arg Thr Leu  
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 Pro Ser Val Val Ser Phe His Leu Lys Arg Phe Glu His Ser Ala Leu  
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 660 665 670  
 Phe Ser Leu Tyr Ala Val Val Asn His Val Gly Thr Ile Asp Thr Gly  
 675 680 685  
 His Tyr Thr Ala Tyr Val Arg His Gln Lys Asp Thr Trp Val Lys Cys  
 690 695 700

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 <213> Drosophila melanogaster

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 35 40 45  
 Trp Ala Trp His Val Val Lys Ser Thr Ser Val Glu Pro Thr Met Phe  
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 Cys Arg Asn Leu Asn Lys Pro Glu Asn Glu Glu Phe Arg Thr Lys Ala  
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 115 120 125  
 Val Phe Pro Ile Ile Leu Ala Leu Phe Leu Gly Ser Phe Ser Asp Arg  
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 Arg Gly Arg Lys Leu Pro Leu Leu Met Gly Leu Val Gly Lys Phe Phe  
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 Tyr Ser Thr Met Ile Val Val Asn Ala Arg Met Thr Thr Trp Pro Val  
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 Ser Leu Gln Gln Arg Thr Ile Arg Val Thr Ile Leu Asp Val Ile Tyr  
 210 215 220  
 Leu Ser Ala Met Pro Met Gly Val Ala Leu Gly Ser His Leu Phe Tyr  
 225 230 235 240  
 Asn Val Phe Asn Gln Ser Tyr Ala Asp Met Phe Thr Val Asn Ala Ser  
 245 250 255

Leu Leu Ala Leu Ala Ile Ile Tyr Thr Leu Cys Ala Leu Lys Trp Gln  
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 275 280 285  
 Trp Gly Asp Phe Phe Asp Lys Gln His Val Lys Asp Ser Leu Ala Val  
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 325 330 335  
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 340 345 350  
 Ser Asn Phe Lys Thr Phe Lys Ser Ser Ala Tyr Val Ile Ala Met Leu  
 355 360 365  
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 370 375 380  
 Ile Ile Phe Ile Gly Thr Trp Ala His Ser Ile Ala Arg Leu Phe Phe  
 385 390 395 400  
 Tyr Phe Ala Thr Asn Thr Asp Leu Leu Tyr Ala Gly Ala Val Val Cys  
 405 410 415  
 Ser Leu Gly Pro Ile Val Gly Pro Met Ile Arg Ala Met Thr Ser Lys  
 420 425 430  
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 Cys Asp Asn Ala Val Pro Phe Ile Ser Gly Val Cys Tyr Ser Gln Leu  
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 485 490 495  
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<213> Drosophila melanogaster

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<400> 14

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 Arg His Ser Gln Arg Arg Arg Lys His His His Ser Gly Pro Gly Gly  
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 Val Gly Gly Gly Ala Gly Lys Asp Asn Val Ser Glu Lys Gln Gln Glu  
 85 90 95  
 Val Glu Arg Pro Val Thr Pro Pro Ala Gln Arg Val Gln Phe Ile Leu  
 100 105 110  
 Gly Glu Asp Val Asp Asp Gly Thr His Val Ser His Pro Leu Phe Ser  
 115 120 125  
 Glu Met Gly Met Leu Val Lys Glu Gly Asp Glu Ile Glu Trp Lys Glu  
 130 135 140  
 Thr Ala Arg Trp Ile Lys Phe Glu Glu Asp Val Glu Glu Gly Gly Asn  
 145 150 155 160  
 Arg Trp Ser Lys Pro His Val Ala Thr Leu Ser Leu His Ser Leu Phe  
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 Lys Lys Lys Lys Ser Asn Ser Lys His Ser Arg Pro Ala Gln Asn Leu  
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Val Pro Thr Arg Phe Val Phe Ile Leu Leu Gly Pro Pro Gly Ser Gln  
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 Ser Asn Phe His Glu Ile Gly Arg Ala Met Ala Thr Leu Met Ser Asp  
 370 375 380  
 Glu Ile Phe His Glu Val Ala Tyr Arg Ala Arg Lys Arg Asp His Leu  
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 Gly Glu Trp Asp Pro Thr Ile Arg Ile Glu Pro Pro Ala Ala Ile Pro  
 420 425 430  
 Ser Gln Glu Val Arg Lys Arg Pro Pro Glu Leu Pro Lys Glu Glu Val  
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 Arg Thr Gly Arg Leu Phe Gly Gly Leu Ile Asn Asp Ile Lys Arg Lys  
 465 470 475 480  
 Ala Pro Trp Tyr Ile Ser Asp Tyr Lys Asp Ala Leu Ser Met Gln Cys  
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 Val Ala Ser Trp Ile Phe Leu Tyr Phe Ala Cys Leu Ser Pro Ile Ile  
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 645 650 655  
 Ala Ser Val Ile Asp Tyr Ala Lys Tyr Asn Trp Asp Ser Cys Glu Ser  
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 Tyr Asn Gly Thr Leu Val Gly Gly Asp Cys Gly Thr Pro Pro Thr Glu



675	680	685
Asn Val Phe Leu Met Ser Val Val Leu Cys Ala Gly Thr Phe Leu Ile 690 695 700		
Ser Thr Val Leu Lys Glu Phe Lys Asn Ala Leu Phe Phe Pro Ser Ile 705 710 715 720		
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Met Ser Phe Phe Asp Tyr Ser Leu Gly Val Pro Thr Gln Lys Leu Glu 740 745 750		
Val Pro Asn Glu Leu Lys Pro Thr Leu Ser Thr Arg Gly Trp Leu Ile 755 760 765		
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Phe Pro Ala Leu Leu Gly Thr Ile Leu Ile Phe Met Asp Gln Gln Ile 785 790 795 800		
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Gly Tyr His Leu Asp Leu Phe Ile Leu Ser Ile Leu Ile Ala Ile Cys 820 825 830		
Ser Met Met Gly Leu Pro Trp Phe Val Ala Ala Thr Val Leu Ser Ile 835 840 845		
Asn His Val Asn Ser Leu Lys Leu Glu Ser Glu Cys Ser Ala Pro Gly 850 855 860		
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Val Ala Ser Leu Lys Gly Leu Gln Phe Phe Asp Arg Ile Leu Ile Met 915 920 925		
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Pro Ile Lys Arg Val His Leu Phe Thr Met Ile Gln Leu Ala Cys Leu 945 950 955 960		
Ile Ile Leu Trp Leu Ile Lys Ser Phe Ser Gln Thr Ser Ile Leu Phe 965 970 975		
Pro Leu Met Leu Val Val Met Ile Gly Ile Arg Lys Ala Leu Asp Leu 980 985 990		
Val Phe Thr Arg Arg Glu Leu Lys Ile Leu Asp Asp Ile Met Pro Glu 995 1000 1005		

Met Thr Lys Arg Ala Ala Ala Asp Asp Leu His Lys Leu Asp Ala  
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Glu Val Gly Leu Leu Ala Arg Ile Phe Pro Trp Gly Lys Gly Ser  
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Arg Ser Arg Val Val Thr Lys Pro Pro Gly Leu Asp Asp Gly Ile  
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Val Gly Ser Gly Gly Ala Val Gly Ala Gly Leu Ile Thr Cys Thr  
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<211> 550

<212> PRT

<213> *Drosophila melanogaster*

<400> 16

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 Trp Gln Val Thr Ile Gly Arg Arg Ile Gly Leu Tyr Arg Phe Cys Gly  
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 Asp Ile Gly Arg Gly Asn Phe Ser Lys Val Lys Leu Ala Val His Gln  
 50 55 60  
 Leu Thr Arg Asp Lys Val Ala Ile Lys Val Val Asp Leu Asp Arg Ala  
 65 70 75 80  
 Gly Leu Asp Ala Lys Ala Leu Arg Met Leu Ser Ser Glu Ile Ala Thr  
 85 90 95  
 Leu Glu Cys Val His His Pro Asn Ile Leu Arg Leu Phe Glu Val Val  
 100 105 110  
 Glu Thr Leu Gly Arg Val Tyr Leu Val Thr Glu Trp Ile Arg Gly Gly  
 115 120 125  
 Glu Leu Tyr Asn His Ile Thr Gln Gly Gly Pro Leu Arg Glu Ile His  
 130 135 140  
 Ala Ala Pro Leu Leu Lys Gln Leu Leu Leu Ala Val Lys His Met His  
 145 150 155 160  
 Ser Leu Gly Tyr Val His Arg Asp Ile Lys Ala Glu Asn Val Leu Leu  
 165 170 175

Leu Ser Glu Asp Arg Leu Lys Leu Ala Asp Phe Gly Phe Ser Thr Gln  
 180 185 190  
 Leu Ile Asn Gly Thr Gly Ala Asn Gln Lys Leu Asp Thr Phe Cys Gly  
 195 200 205  
 Ser Pro Pro Tyr Ala Ala Pro Glu Leu Phe Ser Asp Asp His Tyr Ile  
 210 215 220  
 Gly Ala Pro Val Asp Val Trp Ala Leu Gly Ile Leu Leu Tyr Phe Met  
 225 230 235 240  
 Val Val Gly Asn Met Pro Phe Arg Ala Pro Thr Ile Pro Gly Leu Lys  
 245 250 255  
 Ala Ala Ile Leu Lys Gly Asp Tyr Leu Leu Pro Gly Gln Leu Ser Leu  
 260 265 270  
 Pro Cys Ile Arg Leu Ile Gln Arg Ile Leu Ile His Ile Pro Ala Gln  
 275 280 285  
 Arg Pro Thr Ile Asp Asp Met Leu Asn Ser Gln Phe Val Thr Cys Pro  
 290 295 300  
 Lys Leu Ser Ala Asp Leu Met Gln Trp Glu Ile Asn Gln His Thr Lys  
 305 310 315 320  
 Pro Val Lys Arg Ser Ile Phe Trp Val Arg Ser Lys Ser His Arg Leu  
 325 330 335  
 Arg Lys Ser Ala Ser Leu Arg Asp Arg Tyr Ala Glu Val Val Lys Lys  
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 Pro Ala Ile Ser Met Asn Thr Arg Gln Gln Asp Glu Met Phe Val Gln  
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 Asn Phe Leu Gln Pro Ile Glu Met Gly His Glu Leu Leu Val Pro Val  
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 Ser Ser Gln Leu Lys Glu Pro Gln Ser Thr Glu Gln Ala Lys Arg Pro  
 385 390 395 400  
 Thr Arg Arg Tyr Met Phe Cys Gly Ser Leu Lys Lys Lys Val Thr Pro  
 405 410 415  
 Met Glu Thr Glu Pro Glu Lys Gln Leu Ala Asn Gly Gly Gln Ser Ile  
 420 425 430  
 Gly Ser Ala Lys Ile Asn Pro Trp Asn Val Glu Val Ala Glu Asp Cys  
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 Pro Leu Phe Lys Asn Tyr Asp Ala Glu Thr Gly Ser Cys Val Met Leu  
 450 455 460  
 Pro Thr Asn Thr Glu Asp Leu Ser Gln Leu Gly Ala Leu Glu Phe Glu  
 465 470 475 480  
 Ala Arg Gln Ile Leu Ala Glu Leu Gly Leu Thr Ser Glu Met Leu Ile  
 485 490 495  
 Asn Ala Arg Gln Ser Gly Pro Arg Ser Asp Ile Ile Gly Ala Tyr Arg

500

505

510

Ile Val Val Asn Arg Leu Gln Lys Gln Ser Trp Leu Ala Arg Lys His  
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Val Glu Met Ala Leu His Ser Glu Pro Lys Val Glu Lys Arg Ile Glu  
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Arg Ser Cys Cys Ile Leu  
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 <211> 510  
 <212> DNA  
 <213> Drosophila melanogaster

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 <211> 169  
 <212> PRT  
 <213> Drosophila melanogaster

<400> 18

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Gly Lys Val Val Leu Val Val Asn Ile Ala Ser Lys Cys Gly Leu Thr  
 35 40 45

Lys Asn Asn Tyr Glu Lys Leu Thr Asp Leu Lys Glu Lys Tyr Gly Glu  
 50 55 60

Arg Gly Leu Val Ile Leu Asn Phe Pro Cys Asn Gln Phe Gly Ser Gln  
 65 70 75 80

Met Pro Glu Ala Asp Gly Glu Ala Met Val Cys His Leu Arg Asp Ser  
 85 90 95

Lys Ala Asp Ile Gly Glu Val Phe Ala Lys Val Asp Val Asn Gly Asp  
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 Asn Ala Ala Pro Leu Tyr Lys Tyr Leu Lys Ala Lys Gln Thr Gly Thr  
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 Leu Gly Ser Gly Ile Lys Trp Asn Phe Thr Lys Phe Leu Val Asn Lys  
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 Glu Gly Val Pro Ile Asn Arg Tyr Ala Pro Thr Thr Asp Pro Met Asp  
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 <211> 4491  
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 <213> *Drosophila melanogaster*

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<210> 20
<211> 1496
<212> PRT
<213> Drosophila melanogaster

<400> 20

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Tyr His His Arg Tyr Ala Ser Asn Gly Lys Leu Pro Arg Ala Ala Ala

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Thr Val Asp Val His His Gln Leu Gly Gly Gly Gly Gly Gly Ala Ala		
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Ala Ala Ala Lys Gln Leu Met Ala Asn Gly Ile Ser Gly His Ser Arg		
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Ser Ser Ser Met Ser His Asn Ile His Ala Ala Ala Tyr Ser Glu Leu		
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Ser Ala Ala Pro Pro Ala Phe Ala Thr Pro Pro Thr Arg Arg Arg Phe		
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Phe Asn His Lys Asn Leu Arg Ser Ala Leu Thr Gly Gly Ser Gly Gly		
	115	125
Gly Ser Gly Val Gly Gly Gly Val Gly Gly Ala Gly Gly Val Gly Gly		
	130	140
Gly His Arg Arg Thr Ala Ser Asn Gly Gly Cys Pro Ile Asp Thr Ala		
145	150	155
Ser Ile Leu Ser Gly Asp His Thr His Gln His His His Arg Asp Asn		
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Gln Pro Glu Gly Lys Glu Ser Asn Ala Leu Asn Thr Ser Thr Cys Ser		
	180	190
Asp Ser Ala Val Thr Arg Arg Arg Arg Lys Asn Val Ser Asn His Asn		
	195	205
Leu Lys Thr Ser Ala Arg His Gly Ala Ser Ser Glu Asn Arg Leu Asn		
	210	220
Arg Leu Ser Leu Ala Gly Thr Ser Val Tyr Ala Gly His Leu Ser Ser		
225	230	235
Leu Val Phe Gly Lys Ile Lys Ser Leu Trp Ser Val Asn Ser Ser Asn		
	245	255
Ser Ser Glu Ala Gly Leu Asn Gln Leu Ala Gly Met Asp Pro Ile Leu		
	260	270
Leu Arg Ser Asp Ala Ile Asp His His Ser Ser Phe Leu Asn Glu Lys		
	275	285
Leu Gln Lys Asp Gln Leu His Ala Arg Leu Gly Leu Leu Leu Asn Asp		
	290	300
Pro Gly Ser Asn Gly Asn Ser Ser Ser Ser Gly Ser Gly Cys Glu Pro		
305	310	315
Ile Ser Ala His Ser Thr Thr Ser Thr Thr Ser Ser Ser Gly Val Gly		
	325	335
Ala Ala Ser Thr Thr Thr Ser Gly Ser Ser Gln Asn Val Ser Pro Glu		
	340	350

Gln Thr Leu Ala Ser Gly Ala Gly Met Leu Ser Gly Ser Gln Leu Ser  
 355 360 365  
 Val Ala Thr Ser His Gly Val Lys Glu Asp Ala Leu Ser Leu Cys Gly  
 370 375 380  
 Lys Phe Lys Ala Gly Cys Ser Met Leu His Val Tyr Glu Ala Leu Pro  
 385 390 395 400  
 Ser Lys Ser Arg Lys Gly Asn Val Arg Arg Ser Thr Arg Gly Gln Gln  
 405 410 415  
 Gly Ser Ser Ser Ser Ala Ser Ala Ala Ser Ala Val Gly Ser Arg Val  
 420 425 430  
 Thr Ala Ser Ser Leu Ala Ala Val Gln Leu Ala Leu Lys Pro Leu Phe  
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 Phe Glu Val Pro Leu Gln Glu Pro Asp Pro Pro Tyr Val Gly Arg Gln  
 450 455 460  
 Trp Leu Val Gln Gln Leu Ser Asn Ile Leu Leu Gly Thr Glu Thr Arg  
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 Val Val Leu Ile Asn Gly Gln Pro Gly Thr Gly Lys Thr Ala Phe Cys  
 485 490 495  
 Leu Gln Leu Val Glu Tyr Ser Cys Phe Gly Arg Arg Gln Met Gln Asp  
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 Asp Pro Asp Gly Ile Tyr Ser Gln Leu Gln Leu Gly Ala His Cys Glu  
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 Arg Met Arg Gly Leu Ala Ser His Met Val Gly Tyr His Phe Cys Gln  
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 Ala Asp Ala Asn Leu Thr Cys Gln Val Pro Asp Phe Val His Ser Leu  
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 Ala Ala Gln Leu Cys Gln Ala Pro Gln Leu Thr Ala Tyr Arg Asp Tyr  
 565 570 575  
 Leu Leu Ser Glu Pro His Leu Gln Asp Ile Leu Ser Val Arg Glu Cys  
 580 585 590  
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 Ala His Leu His Arg Ala Gly Lys Ile Pro Ala Lys Val Ala Val Ile  
 610 615 620  
 Val Val Asp Ala Leu Cys Glu Ala Glu Tyr His Arg Pro Asp His Gly  
 625 630 635 640  
 His Thr Ile Ala Ser Phe Leu Ala Gln Leu Thr Pro His Phe Pro Ala  
 645 650 655  
 Trp Leu Lys Leu Val Ala Thr Val Arg Thr Gln Met Leu Glu Leu Val  
 660 665 670

Lys Ala Pro Ser Tyr Thr Gln Leu Thr Leu Asp Ser Trp Ala Ser Ser  
 675 680 685  
 Gln Ala Leu Gln Gln Asp Met Leu Asp Tyr Ile Gly Ala Arg Leu Ala  
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 Asp Ser Pro Glu Ile Arg Met Asn Ile Gly Gly Gly Gly Gly Gln Asn  
 705 710 715 720  
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 Ser Leu Ser Arg Gly Ser Met Leu Tyr Ala Lys Leu Ile Leu Asp Leu  
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 Pro Val Ser Leu Ala Gln Ile Phe Leu Leu His Phe Asn Leu Arg Phe  
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 Glu Ala Leu Ser His Gly Arg Glu Ala Leu Ser Trp Pro Asp Phe Met  
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 Gln Arg Phe Lys Leu Leu Asp Gly Phe Leu Ile Lys Arg Leu Asp Asn  
 835 840 845  
 Thr Tyr Met Phe Phe His Ser Ser Leu Arg Glu Trp Leu Met Arg Arg  
 850 855 860  
 Asp Glu Gly Glu Ser Asn Lys Phe Leu Cys Asp Ala Arg Leu Gly His  
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 Trp Leu Ala Gly Ala Ala Asp Asn Ile Ser Ser Ser Leu Gly Ala Leu  
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 Arg Asn Val Tyr Ser Pro Asn Leu Lys Val Ser Arg Leu Val Leu Leu  
 945 950 955 960  
 Ala Gly Ala Ser Pro Asn His Arg Thr Asp Tyr Met Gly Gly Ala Pro  
 965 970 975  
 Ile Leu Cys Ile Ala Ala His Glu Gly Ile Leu Pro Met Val Ser Leu  
 980 985 990  
 Leu Leu Glu Phe Gly Ala Asp Val Gly Leu Thr Asn Ser Gln Gly Cys

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Arg Pro	Leu Val Ala Ala	Gly Ser Ser Leu Gly	Gln Leu Asp Ile
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Thr Gln	Arg Cys Ala Leu	Val His Ala Ala Arg	Met Gly His Leu
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Ser Val	Val Lys Tyr Leu	Leu Ala Cys Asp Trp	Ser Pro Arg Pro
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His Ser	Gln Asp Val Thr	Arg Ser Val Ala Leu	Gln Gln Ala Leu
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Ile Gly	Ala Ala Ala Gln	Ala His Cys Lys Ile	Leu Glu Asp Leu
1085		1090	1095
Leu Asp	Leu Asn Glu Thr	Glu Phe Asp Leu Asp	Val Asn Gly Met
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Glu Pro	Ser Ser Gly Glu	Leu Ala Leu Thr Ala	Ala Ala Arg His
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Gly Cys	Ile Asp Val Val	Gly Ile Leu Leu Ser	Arg Gly Ala Gln
1130		1135	1140
Ile Asp	Ala Arg Asn Arg	Gln Gly Tyr Ser Ala	Leu Trp Leu Ala
1145		1150	1155
Val Lys	Glu Gly His Trp	Ser Val Val Glu His	Leu Leu Gln Arg
1160		1165	1170
Gly Ala	Leu Leu Asp Glu	Pro Leu Gly Gln Thr	Arg Lys Thr Pro
1175		1180	1185
Leu Met	Ile Ala Ala Glu	Glu Gly His Leu Glu	Leu Val Asp Leu
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Leu Leu	Ala Arg Gly Ala	Gln Arg Glu Ala Gln	Asp His Glu Gly
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Phe Thr	Ala Leu Ser Trp	Ala Cys Leu Arg Gly	His Leu Ala Ala
1220		1225	1230
Ala Lys	Thr Leu Ile Glu	His Gly Cys Asn Arg	His His Glu Asp
1235		1240	1245
His Asn	Gly Arg Thr Ala	Leu Asp Leu Ala Ala	Tyr Gln Gly Ala
1250		1255	1260
Ala Ser	Leu Val Ile Tyr	Ile Leu Glu Gln Gly	Gly Asn Leu Glu
1265		1270	1275
His Ile	Asp Val His Gly	Met Arg Pro Leu Asp	Arg Ala Ile Ala
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Cys Arg	Asn Ile Gln Ala	Val Gln Val Phe Leu	Arg Lys Gly Ala
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 1370 1375 1380  
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 Thr Glu Leu Leu Thr Arg Ile Ser Ile Ser Ser Glu Asp Gln Thr  
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 Ser His His Glu Ile Thr Asp Leu  
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<210> 21  
 <211> 336  
 <212> DNA  
 <213> *Drosophila melanogaster*

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<210> 22  
 <211> 111

&lt;212&gt; PRT

<213> *Drosophila melanogaster*

&lt;400&gt; 22

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20 25 30

Gln Gly Pro Pro Glu Thr Thr Leu Gly Arg Phe Arg Leu Met Pro Thr  
35 40 45

Ser Asn Tyr Gly Ala Ile Ser Pro Ile Leu Gln Arg Gly Arg Phe Ala  
50 55 60

Val Ile Pro Glu Glu Pro Gln Ala Gly Ser Pro Ala Leu Gly Thr Pro  
65 70 75 80

Pro Pro Gly Gly Arg Thr Ala Arg Ser Pro Ser Pro Glu Trp Asp Phe  
85 90 95

Asp Ile Glu Gln Val Ser Val Pro Ser Ser Ser Ala Gly Ile Asp  
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&lt;210&gt; 23

&lt;211&gt; 1587

&lt;212&gt; DNA

<213> *Drosophila melanogaster*

&lt;400&gt; 23

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<210> 24  
 <211> 528  
 <212> PRT  
 <213> *Drosophila melanogaster*

<400> 24

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Asn Ala Ile Ala Leu Ile Ala Asp Val Ala Thr Leu Pro Leu Pro Leu
          20           25           30

Ser Pro Thr Ala Thr Thr Thr Thr Ala Ala Ser Gly Ala Thr Ala Thr
          35           40           45

Ala Pro Ala Asp Arg Val Glu Trp Ser Arg Ser Thr Ile Leu Asn Phe
          50           55           60

Ile Glu Asp Tyr Arg Arg Gln Arg Val Leu Trp Asp Pro Asn Thr Lys
65           70           75           80

Gly Tyr His Ile Lys Gln Thr Lys Tyr Glu Ala Leu Lys Leu Leu Ser
          85           90           95

Gln Lys Tyr Gly Thr Glu Ile Arg Ser Ile Arg Ser Lys Ile Lys Ser
          100          105          110

Leu Arg Ser Ser Phe His Arg Glu His Gly Lys Val Leu Ser Gly Arg
          115          120          125

Asn Arg Gly Val Ile Tyr Gln Pro Met Trp Phe Ala Tyr Glu Ala Ile
          130          135          140

Arg Phe Ile Leu Asp Gly Glu Arg Asp Gln Asp Arg Asp Gln Asp Gln

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145	150	155	160
Asp Gln Asp Ala Glu Thr Glu Thr Glu Val Asp Glu Lys Leu Ala Leu	165	170	175
Met His Ser Leu Asp Leu Glu Gln Leu Lys Ala Asp Lys Leu Val Asp	180	185	190
Arg Asp Ile Ile Leu Gln Val Glu Gln Gln Gln Gln His Asp Glu	195	200	205
Leu Thr Ala Arg Ile Ala Ala Thr Val Ala Ala Val Ala Ala Ala Ala	210	215	220
Ala Ala Ala Asn Ala Arg Asp Arg Glu Arg Asp Val Asp Thr Ala Gly	225	230	235
Asp Met Asp Thr Thr Arg Glu Leu Glu Leu Glu Glu Ala Ala Val Gly	245	250	255
Gly Gly Leu Ile Glu Ser Ser Ser Ala Ala Val Leu Gly Met Leu Asp	260	265	270
Arg Arg Thr Ser Thr Pro Ser Pro Ile Asn Tyr Tyr Lys Pro Thr Asp	275	280	285
Leu Thr Tyr Asn His Arg Lys Arg Lys Ala Met Gly Val Glu His Val	290	295	300
Val Gly Ala Leu Thr Leu Thr Pro Ile Lys Val Val Gly Gly Ala Val	305	310	315
Gly Ala Gly Thr Val Gly Ser Ala Gly His Gln Gln Gln Gln Gln His	325	330	335
Gln Gln Gln Gln Met Asn His Ser Gln Leu Ala Phe Gln Ala Leu Gln	340	345	350
Gln His Phe Ser His Asn His Gly Leu Ser Leu Ser His Cys Asn Gly	355	360	365
Gln Pro Gln Gln Gln Gln Gln Gln His Gln His Gln Pro His His Gln	370	375	380
Gln Gln Gln Gln Gln Gln Ala Leu His Leu Gln His Gln Gln Gln Gln	385	390	395
Gln His Ser Ser Asn Met Ala Gln Lys Arg Asp Arg Asp Arg Asp Leu	405	410	415
Ser Thr Ser Asn Gly Asn Gly Asn Ser Ser Asn Thr Asn Asn Thr Ser	420	425	430
Leu Glu Pro Ile Ala Thr Ser Ser Asn Cys Ser Ser Ser Ser Ser Asn	435	440	445
Asn Ser Ala Ala Thr Pro Pro Lys Pro Leu Leu Gly Gly Gly Gly Leu	450	455	460
Ser Ala Asn His Val Asp Glu Tyr Gly Val Phe Gly Glu Tyr Val Ala	465	470	475
			480



Ile Thr Ile Arg Lys Leu Lys Thr Ser Lys Ser Lys Ile Val Val Lys  
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<210> 25

<211> 2715

<212> DNA

<213> Drosophila melanogaster

<400> 25

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<210> 26
<211> 904
<212> PRT
<213> Drosophila melanogaster

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<400> 26

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          20           25           30

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 65 70 75 80  
 Ala Leu Lys Pro Thr Glu Pro Ser Ile Ser Asn Gly His Glu Val Thr  
 85 90 95  
 Thr Ala Val Ala Ala Met Lys Ser Gln Ala Glu Val Pro Leu Pro Pro  
 100 105 110  
 Thr Ala Ser Ala Ala Ile Pro Glu Asp Ser Ile Ala Arg Leu Glu Val  
 115 120 125  
 Val Thr Ser Ala Val Pro Cys Glu Pro Trp Thr Ser Asn Gly Pro Thr  
 130 135 140  
 Thr Pro Ser Ala Val Ala Gly Pro Ala Ala Ser Ala Glu Pro Val Asp  
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 Cys Ile Ser Lys Leu Gln Ala Val Ala Val Pro Ser Asp Pro Trp Gly  
 165 170 175  
 Ser Ile Ala Thr Arg Ser Thr Leu Ala Thr Thr Leu Leu Ser Ala Asp  
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 Glu Leu Asp Asp Asp Asp Asp Phe Glu Asp Asp Tyr Glu Glu Glu  
 195 200 205  
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 Ala Thr Ala Gly Ser Ser Pro Ala Asn Pro Ser Ser Gly Ala Gln Gln  
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 Phe Tyr Glu Pro Thr Asn Gly Gly Ala Tyr Ala Pro Pro Ala Ala Pro  
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Cys Ser Ala Asn Arg Ser Cys Tyr Lys Asp Thr Arg Leu Lys Ile Arg 420 425 430																		
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Gln Gln Ser Pro Pro Ala Pro Leu His Pro His Thr Gln Gln Gln Met 515 520 525																		
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&lt;210&gt; 27

&lt;211&gt; 4674

&lt;212&gt; DNA

<213> *Drosophila melanogaster*

&lt;400&gt; 27

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Thr Pro Ala Lys Pro Ser Lys 1355	Glu Asn Arg Phe Leu 1360	Gly Ser Pro 1365
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<213> *Drosophila melanogaster*

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 Gly Arg Pro Ile Val Leu Arg Ala Asn His Phe Gln Val Thr Met Pro  
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 Leu Tyr Thr Arg Asp Pro Leu Pro Ile Gly Asn Glu Arg Leu Glu Leu  
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<213> Drosophila melanogaster

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35          40          45
Asp Gln Asp Ala Asp Leu Asp Thr Leu Lys Ala Ala Ala Thr Gly Met
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Arg Thr Arg Ser Gly Arg Thr Ala Arg Leu Ile Val Thr Ala Ala Gln
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<213> *Drosophila melanogaster*

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35          40          45
Leu Arg Asp Tyr Tyr Phe Ala Leu Ala Asn Thr Val Lys Asp Asn Met
50          55          60
Val Gly Arg Trp Ile Arg Thr Gln Gln His Tyr Tyr Glu Lys Asp Pro
65          70          75          80
Lys Arg Val Tyr Tyr Leu Ser Leu Glu Tyr Tyr Met Gly Arg Ser Leu
85          90          95
Thr Asn Thr Met Ile Asn Leu Gly Ile Gln Ser Glu Cys Glu Glu Ala
100         105         110
Met Tyr Gln Leu Gly Leu Asp Ile Glu Asn Leu Glu Glu Met Glu Glu
115         120         125
Asp Ala Gly Leu Gly Asn Gly Gly Leu Gly Arg Leu Ala Ala Cys Phe

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 <212> PRT  
 <213> *Drosophila melanogaster*

<400> 36

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 20 25 30

Gly Ala Ala Thr Pro Pro Thr Ser Gly Pro Pro Thr Pro Asn Asn Asn

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Ser Asn Asn Gly Ser Asp Pro Ser Ile Gln Gln Gln Gln Asn Val		
50	55	60
Ala Pro His Pro Tyr Gly Ala Pro Pro Pro Pro Gly Ser Gly Pro Gly		
65	70	75 80
Gly Pro Pro Gly Pro Asp Pro Ala Ala Val Met His Tyr His His Leu		
	85	90 95
His Gln Gln Gln Gln Gln His Pro Pro Pro Pro His Met Gln Gln Gln		
	100	105 110
Gln His His Gly Gly Pro Ala Pro Pro Pro Pro Gly Gly Ala Pro Glu		
	115	120 125
His Ala Pro Gly Val Lys Glu Glu Tyr Thr His Leu Pro Pro Pro His		
	130	135 140
Pro His Pro Ala Tyr Gly Arg Tyr His Ala Asp Pro Asn Met Asp Pro		
145	150	155 160
Tyr Arg Tyr Gly Gln Pro Leu Pro Gly Gly Lys Pro Pro Gln Gln Gln		
	165	170 175
Gln Pro His Pro Gln Gln Gln Pro Pro Gln Gln Pro Gly Pro Gly Gly		
	180	185 190
Ser Pro Asn Arg Pro Pro Gln Gln Arg Tyr Ile Pro Gly Gln Pro Pro		
	195	200 205
Gln Gly Pro Thr Pro Thr Leu Asn Ser Leu Leu Gln Ser Ser Asn Pro		
	210	215 220
Pro Pro Pro Pro Gln His Arg Tyr Ala Asn Thr Tyr Asp Pro Gln Gln		
225	230	235 240
Ala Ala Ala Ser Ala Ala Ala Ala Ala Ala Ala Gln Gln Gln Gln Ala		
	245	250 255
Gly Gly Pro Pro Pro Pro Gly His Gly Pro Pro Pro Pro Gln His Gln		
	260	265 270
Pro Ser Pro Tyr Gly Gly Gln Gln Gly Gly Trp Ala Pro Pro Pro Arg		
	275	280 285
Pro Tyr Ser Pro Gln Leu Gly Pro Ser Gln Gln Tyr Arg Thr Pro Pro		
	290	295 300
Pro Thr Asn Thr Ser Arg Gly Gln Ser Pro Tyr Pro Pro Ala His Gly		
305	310	315 320
Gln Asn Ser Gly Ser Tyr Pro Ser Ser Pro Gln Gln Gln Gln Gln Gln		
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Gln Gln Gln Gln Gln Gln Gln Ala Gly Gln Gln Pro Gly Gly Pro Val		
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Pro Gly Gly Pro Pro Pro Gly Thr Gly Gln Gln Pro Pro Gln Gln Asn		
	355	360 365

Thr Pro Pro Thr Ser Gln Tyr Ser Pro Tyr Pro Gln Arg Tyr Pro Thr  
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 Thr His Gln Tyr Pro Glu Pro Asn Arg Pro Trp Pro Gly Gly Ser Ser  
 405 410 415  
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 Tyr Pro Met Pro Pro His Met His Gly Gly Tyr Lys Met Gly Gly Pro  
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 Gly Gln Ser Pro Gly Ala Gln Gly Tyr Pro Pro Gln Gln Pro Gln Gln  
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 660 665 670  
 Tyr Ala Thr Gly Pro Pro Pro Pro Pro Thr Ser Gln Ala Gly Ala Gly  
 675 680 685



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 690 695 700  
 Arg Gly Met Pro Asn His Thr Gly Gln Tyr Pro Pro Tyr Gln Trp Val  
 705 710 715 720  
 Pro Pro Ser Pro Gln Gln Thr Val Pro Gly Gly Ala Pro Gly Gly Ala  
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 Met Val Gly Asn His Val Gln Gly Lys Gly Thr Pro Pro Pro Pro Val  
 740 745 750  
 Val Gly Gly Pro Pro Pro Pro Gln Gly Ser Gly Ser Pro Arg Pro Leu  
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 Asn Tyr Leu Lys Gln His Leu Gln His Lys Gly Gly Tyr Gly Gly Ser  
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 Pro Thr Pro Pro Gln Gly Pro Gln Gly Tyr Gly Asn Gly Pro Thr Gly  
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 Met His Pro Gly Met Pro Met Gly Pro Pro His His Met Gly Pro Pro  
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 820 825 830  
 Gln Met Leu Gln Gly Gly Gln Pro Gln Gly Gln Gly Ala Ser Gly Gly  
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 Ser Ser Gly Pro Thr Gly Ala Ala Gly Met His Ala Val Thr Ser Val  
 865 870 875 880  
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 885 890 895  
 Ser Thr Leu Ser Asn Ala Ser Ala Ala Ser Gly Glu Asp Pro Gln Cys  
 900 905 910  
 Thr Thr Pro Lys Ser Arg Lys Asn Asp Pro Tyr Ser Gln Ser His Leu  
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 Ala Pro Pro Ser Thr Ser Pro His Pro Val Val Met His Pro Gly Gly  
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 Gly Pro Gly Glu Glu Tyr Asp Met Ser Ser Pro Pro Asn Trp Pro Arg  
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 Pro Ala Gly Ser Pro Gln Val Phe Asn His Val Pro Val Pro Gln Glu  
 965 970 975  
 Pro Phe Arg Ser Thr Ile Thr Thr Thr Lys Lys Ser Asp Ser Leu Cys  
 980 985 990  
 Lys Leu Tyr Glu Met Asp Asp Asn Pro Asp Arg Arg Gly Trp Leu Asp  
 995 1000 1005  
 Lys Leu Arg Ala Phe Met Glu Glu Arg Arg Thr Pro Ile Thr Ala

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Cys Pro Thr Ile Ser Lys Gln 1025	Pro Leu Asp Leu Tyr 1030	Arg Leu Tyr 1035
Ile Tyr Val Lys Glu Arg Gly 1040	Gly Phe Val Glu Val 1045	Thr Lys Ser 1050
Lys Thr Trp Lys Asp Ile Ala 1055	Gly Leu Leu Gly Ile 1060	Gly Ala Ser 1065
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Leu Thr Phe Glu Cys His Phe 1085	Asp Arg Gly Asp Ile 1090	Asp Pro Leu 1095
Pro Ile Ile Gln Gln Val Glu 1100	Ala Gly Ser Lys Lys 1105	Lys Thr Ala 1110
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Ser Phe Pro Ala Pro Pro Gly 1130	Ser Ala Pro Asn Ala 1135	Ala Ile Asp 1140
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Gly Pro Gly Gln Val Pro Pro 1310	Ser Pro Gln Gln His 1315	Val Arg Pro 1320

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Pro Val	Ser Arg Thr Pro	Gly Ser Pro Tyr Pro	Ser Gln Pro Gly
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Ser Ser	Ala Tyr Pro Thr	Gly Arg Pro Ser Gln	Gln Asp Tyr Tyr
1445		1450	1455
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1460		1465	1470
Phe Ile	Lys Asp Ser Gln	Pro Tyr Pro Gly Tyr	Asn Ala Arg Pro
1475		1480	1485
Gln Ile	Tyr Gly Ala Trp	Gln Ser Gly Thr Gln	Gln Tyr Arg Pro
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Gln Tyr	Pro Ser Ser Pro	Ala Pro Gln Asn Trp	Gly Gly Ala Pro
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Met Asn	Pro Gly Gln Thr	Ala Gln Ser Gly Ile	Ala Pro Pro Gly
1595		1600	1605
Ser Pro	Leu Arg Pro Pro	Ser Gly Pro Gly Gln	Gln Asn Arg Met
1610		1615	1620

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1640						1645					1650		Pro
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1655						1660					1665		Pro
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1670						1675					1680		Gln
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1685						1690					1695		Pro
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1715						1720					1725		His
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1730						1735					1740		Gly
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1775						1780					1785		Pro
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1910						1915					1920		Asp
Glu	Gly	Ile	Asp	Leu	Gly	Gln	Val	Arg	Val	Gln	Pro	Asn	Pro
													Glu

1925					1930					1935				
Glu Arg Ser Leu Leu Leu	Ser Phe Thr Pro Asn Tyr	Thr Met Val	1940	1945	1950									
Thr Arg Lys Gly Val Pro	Val Arg Ile Gln Pro	Ala Glu Asn Asp	1955	1960	1965									
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Arg Leu Tyr Glu Gln Leu	Glu Pro Val Gly Ser	Asp Ala Trp Thr	1985	1990	1995									
Tyr Gly Phe Thr Glu Pro	Asp Pro Leu Asp Gly	Ile Ile Asp Val	2000	2005	2010									
Phe Lys Ser Glu Ile Val	Asn Ile Pro Phe Ala	Arg Tyr Ile Arg	2015	2020	2025									
Ser Asp Lys Lys Gly Arg	Lys Arg Thr Glu Leu	Ala Ser Ser Ser	2030	2035	2040									
Arg Lys Pro Glu Ile Lys	Thr Glu Glu Asn Ser	Thr Glu Glu Gln	2045	2050	2055									
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Gln Gln Arg Leu Thr Asn	Gly Val Ala Pro Cys	Ser Ser Thr Pro	2120	2125	2130									
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Leu Ala Arg Arg Cys Ile	Ala Leu Ser Asn Ile	Phe Arg Asn Leu	2180	2185	2190									
Thr Phe Val Pro Gly Asn	Glu Thr Val Leu Ala	Lys Ser Thr Arg	2195	2200	2205									
Phe Leu Ala Val Leu Gly	Arg Leu Leu Leu Leu	Asn His Glu His	2210	2215	2220									
Leu Arg Arg Thr Pro Lys	Thr Arg Asn Tyr Asp	Arg Glu Glu Asp	2225	2230	2235									

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2270						2275					2280			
Glu	Leu	Ile	Ala	Arg	Pro	Leu	Ile	Asp	Gly	Leu	Leu	His	Trp	Ala
2285						2290					2295			
Val	Cys	Pro	Ser	Ala	His	Gly	Gln	Asp	Pro	Phe	Pro	Ser	Cys	Gly
2300						2305					2310			
Pro	Asn	Ser	Val	Leu	Ser	Pro	Gln	Arg	Leu	Ala	Leu	Glu	Ala	Leu
2315						2320					2325			
Cys	Lys	Leu	Cys	Val	Thr	Asp	Ala	Asn	Val	Asp	Leu	Val	Ile	Ala
2330						2335					2340			
Thr	Pro	Pro	Phe	Ser	Arg	Leu	Glu	Lys	Leu	Cys	Ala	Val	Leu	Thr
2345						2350					2355			
Arg	His	Leu	Cys	Arg	Asn	Glu	Asp	Gln	Val	Leu	Arg	Glu	Phe	Ser
2360						2365					2370			
Val	Asn	Leu	Leu	His	Tyr	Leu	Ala	Ala	Ala	Asp	Ser	Ala	Met	Ala
2375						2380					2385			
Arg	Thr	Val	Ala	Leu	Gln	Ser	Pro	Cys	Ile	Ser	Tyr	Leu	Val	Ala
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Phe	Ile	Glu	Gln	Ala	Glu	Gln	Thr	Ala	Leu	Gly	Val	Ala	Asn	Gln
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His	Gly	Ile	Asn	Tyr	Leu	Arg	Glu	Asn	Pro	Asp	Ser	Met	Gly	Thr
2420						2425					2430			
Ser	Leu	Asp	Met	Leu	Arg	Arg	Ala	Ala	Gly	Thr	Leu	Leu	His	Leu
2435						2440					2445			
Ala	Lys	His	Pro	Asp	Asn	Arg	Ser	Leu	Phe	Met	Gln	Gln	Glu	Gln
2450						2455					2460			
Arg	Leu	Leu	Gly	Leu	Val	Met	Ser	His	Ile	Leu	Asp	Gln	Gln	Val
2465						2470					2475			
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<400> 40

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 Ile Ser Leu Asp Thr Leu Lys Arg Asp Arg Phe Glu Lys Ile Thr Arg

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<211> 3459

<212> DNA

<213> *Drosophila melanogaster*

<400> 41

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<400> 42

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 Ser Lys Glu Asp Val Ala Gln Ala Ser Pro Gln Ala Pro Val Ala Asp  
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 Pro Lys Leu Asp Glu Glu Asp Glu Glu Ala Thr Thr Asn Gly Asp Gly  
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 Asp His Glu Pro Glu Asp Glu Asp Asp Ala Gln Lys Ile Gly Ser Thr  
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 Glu Ser Val Ala Ser Glu Gly Val Val Glu Glu Glu Pro Pro Ala Lys  
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Pro Pro Val Val Lys Ala Ile Pro Pro Pro Pro 305	Val Gln Asp Asp Glu 310		
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Leu Ser Ile Ser Pro Ser Gly Lys Arg Lys Ser Asp Leu Asp Asp Leu 340			
Gln Leu Gln Gln Pro Ser His Lys Arg Gln Arg Ser Ser Thr Pro Ser 355			
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Val Pro Pro Lys Leu Val Pro Met Ala Gly Gly Met Ser Ala Ser Pro 420			
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 Ala Lys Lys Phe Arg Pro Glu Leu Asn Leu Ala Pro Pro Asn Asp Trp  
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 <213> *Drosophila melanogaster*

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<400> 44

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Arg	Ala	Glu	Ser	Val	Glu	Glu	Ser	Pro	Glu	Gln	Gln	Arg	Lys	Leu	Pro	50	55	60	
Thr	Arg	Glu	Pro	Leu	Ala	Lys	Asn	Phe	Phe	Ile	Gly	Val	Val	Asp	Lys	65	70	75	80
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Lys	Leu	Ile	Gly	Thr	Glu	Ala	Ile	Tyr	Glu	Ile	Ser	Pro	Pro	Glu	Glu	195	200	205	
Asp	Tyr	Phe	Asn	Thr	Thr	Ala	Glu	Leu	Phe	Pro	Glu	Tyr	Gly	Lys	Trp	210	215	220	
Gln	Leu	Asn	Gly	Glu	Lys	Ser	Phe	Val	Ile	Cys	Thr	Pro	Gly	Glu	Arg	225	230	235	240
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Val	Leu	Gly	Arg	Gly	Thr	Thr	Ile	Phe	Leu	Val	Asp	Ser	Gln	Gln	Glu	260	265	270	

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 Glu Ile Arg Arg Val His Phe Glu Gly Val Lys Leu Gly Glu Asp Gln  
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 Val Val Gly Leu Pro His Asp Gly Asn Arg Tyr Ser Glu Gln Leu Val  
 305 310 315 320  
 Arg Ser Ser Arg Leu Arg Gly Ser Leu Val Gly Leu Ser Leu Ala Lys  
 325 330 335  
 Lys Leu Leu Asn Glu Leu Ala Gln Tyr Thr Val Asn Thr Thr Gln Cys  
 340 345 350  
 Gly Val Gln Leu Gln Asp Leu Glu Leu Thr Arg Ile His Met Ser Arg  
 355 360 365  
 Ala Met Cys Ser Val Tyr Ala Met Glu Ser Met Leu Tyr Leu Thr Ala  
 370 375 380  
 Gly Leu Leu Asp Glu Phe Arg Ala Gln Asp Val Thr Leu Glu Ser Ala  
 385 390 395 400  
 Ile Thr Lys Tyr Phe Thr Leu Arg Gln Val Tyr Ala Ile Ala Ser Gln  
 405 410 415  
 Asn Leu Gly Val Val Gly Pro Lys Ser Leu Leu Ser Gly Glu Thr Thr  
 420 425 430  
 Glu Leu Gly Leu Arg Asp Ala Ala Gln Leu Cys Thr Gln Gly Glu Ser  
 435 440 445  
 Leu Asp Thr Leu Gly Met Phe Ile Ala Leu Thr Gly Leu Gln His Ala  
 450 455 460  
 Gly Gln Ala Met Asn Thr Gly Val Arg Lys Ser Arg Asn Pro Leu Phe  
 465 470 475 480  
 Asn Pro Gly His Ile Phe Gly Lys Phe Leu Asp Asn Asn Ser Ile Asp  
 485 490 495  
 Asn Pro Lys Thr Lys Met Gln Leu Ser Glu His Val His Pro Ser Leu  
 500 505 510  
 Glu Ala Ala Ala Gln Cys Ile Glu Leu Ser Val Ala Arg Leu Gln Met  
 515 520 525  
 Ala Val Glu Leu Met Phe Thr Lys His Gly Asn Ala Val Val Glu Arg  
 530 535 540  
 Gln Ser Glu Met Gln Arg Leu Ala Glu Val Gly Thr Leu Ile Tyr Ala  
 545 550 555 560  
 Met Trp Ala Ser Val Ala Arg Ala Ser Arg Ser Tyr Cys Ile Gly Leu  
 565 570 575  
 Pro Leu Ala Asp His Glu Leu Leu Thr Ala Thr Ala Ile Cys Ser Glu  
 580 585 590  
 Gly Arg Asp Arg Val Arg Thr Leu Cys Thr Glu Ile Tyr Gly Gly His

595	600	605	
Phe Val Asn Asn Asp Asn Asn Leu Val Arg Leu Ser Lys Gln Val Ala			
610	615	620	
Lys Ser Lys Gly Tyr Phe Ala Val His Pro Leu Thr Phe Asn Phe			
625	630	635	
<210> 45			
<211> 1467			
<212> DNA			
<213> Drosophila melanogaster			
<400> 45			
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aatctgcccc	aattgcggcc	cgccccctt	acggcagctc tgctgaaggt gtcggccacg 120
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gataacatgg	ctgcatcccc	gcccaggcc	aagaagcgtc gcctggacca tctaacctgg 240
gaggagaaag	tgcaaagaaa	gaagctaaag	aaccgtgtgg ccgcccagac atcgcggtgac 300
cgcaagaagg	cacgcatgga	ggagatggac	tacgagatca aggagctgac agacagaacg 360
gaaatactac	agaacaagtg	cgatagcctg	caggccatca acgagtcact gctggccaag 420
aaccacaagc	tggactcgga	gctggagctg	ctgcgccaaag aactcgccga actgaagcag 480
caacagcagc	acaacaccag	atgcatcagc	caatccaacg ccagcgcagg cgctgagggc 540
tggtatacaa	caggtggaca	cacagtcgtc	agcgcgtctg ctggcggagc agctgaagag 600
cagcaagagc	ctggcctcac	tctggaaagt	tgtggccctc tgcttactct acaagacatg 660
cttggcgtcg	acgaagagtt	cgacgtcaag	cgcctcgaag agctggccga aagtctgtc 720
gcagatatca	cagcagacct	ggaaacaggc	gctggagcga gcagcccagc tgctgccccaa 780
gatgcaggca	acgcagagcg	attgcctgga	ccaatggtgg ggcccgcagc agagcgcttg 840
gaatccgacg	ggcatagagc	taatggcctg	aatgttgagc aggaacagga aaccgagcac 900
aaggtcagcc	taaattgtgca	gatgttgaag	ataaatggaa acccacagca taccacagca 960
gcgccagcct	cgagaacagc	cacaatcaca	gcgacagcgg ccgcctcgca actacaggcc 1020
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caggtctatc	tcaacgtgat	gaacgccgtc	gacaattcgg acgacgagga aagcttcgat 1260
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gacgagctgt ttcccagttt gatctga

1467

<210> 46  
 <211> 488  
 <212> PRT  
 <213> *Drosophila melanogaster*

&lt;400&gt; 46

Met Ala Pro Thr Ala Asn Thr Val Leu Ile Thr Val Pro Arg Thr Ala  
 1 5 10 15

Ile Thr Ser Asn Asn Leu Pro Lys Leu Arg Pro Ala Pro Leu Thr Ala  
 20 25 30

Ala Leu Leu Lys Val Ser Ala Thr Pro Ser Ala Ser Pro Thr Pro Ser  
 35 40 45

Ser Ser Gly Tyr Ala Ser Ser Ser Asn Met Asp Asp Asp Asn Met Ala  
 50 55 60

Ala Ser Gln Pro Lys Ala Lys Lys Arg Arg Leu Asp His Leu Thr Trp  
 65 70 75 80

Glu Glu Lys Val Gln Arg Lys Lys Leu Lys Asn Arg Val Ala Ala Gln  
 85 90 95

Thr Ser Arg Asp Arg Lys Lys Ala Arg Met Glu Glu Met Asp Tyr Glu  
 100 105 110

Ile Lys Glu Leu Thr Asp Arg Thr Glu Ile Leu Gln Asn Lys Cys Asp  
 115 120 125

Ser Leu Gln Ala Ile Asn Glu Ser Leu Leu Ala Lys Asn His Lys Leu  
 130 135 140

Asp Ser Glu Leu Glu Leu Leu Arg Gln Glu Leu Ala Glu Leu Lys Gln  
 145 150 155 160

Gln Gln Gln His Asn Thr Arg Cys Ile Ser Gln Ser Asn Ala Ser Ala  
 165 170 175

Gly Ala Glu Gly Trp Tyr Thr Thr Gly Gly His Thr Val Val Ser Ala  
 180 185 190

Ser Ala Gly Gly Ala Ala Glu Glu Gln Gln Glu Pro Gly Leu Thr Leu  
 195 200 205

Glu Ser Cys Gly Pro Leu Pro Thr Leu Gln Asp Met Leu Gly Val Asp  
 210 215 220

Glu Glu Phe Asp Val Lys Arg Leu Glu Glu Leu Ala Glu Ser Leu Leu  
 225 230 235 240

Ala Asp Ile Thr Ala Asp Leu Glu Thr Gly Ala Gly Ala Ser Ser Pro  
 245 250 255

Ala Ala Ala Gln Asp Ala Gly Asn Ala Glu Arg Leu Pro Gly Pro Met  
 260 265 270

Val Gly Pro Ala Ala Glu Arg Leu Glu Ser Asp Gly His Arg Ala Asn  
275 280 285

Gly Leu Asn Val Glu Gln Glu Gln Glu Thr Glu His Lys Val Ser Leu  
290 295 300

Asn Val Gln Met Leu Lys Ile Asn Gly Asn Pro Gln His Thr Thr Ala  
305 310 315 320

Ala Pro Ala Ser Arg Thr Ala Thr Ile Thr Ala Thr Ala Ala Ala Ser  
325 330 335

Gln Leu Gln Ala Thr Pro Asp Thr Val Tyr Gly Thr Tyr Asp Ala Lys  
340 345 350

Thr Asn Ser Ile Thr Ile Val Met Asp Gly Asp Ala Val Pro Val Asn  
355 360 365

Glu Ala Val Glu Glu Ile Tyr Cys Asp Gly Val Ser Ala Gly Asp Asp  
370 375 380

Ser Thr Asp Val Ile Met Lys Cys Pro Pro Pro Ala Thr Ser Pro Ser  
385 390 395 400

Gln Val Tyr Leu Asn Val Met Asn Ala Val Asp Asn Ser Asp Asp Glu  
405 410 415

Glu Ser Phe Asp Pro Ile Asp Arg Phe Leu Arg Pro Arg Val Lys Ala  
420 425 430

Ile Ser Pro Leu Ala Lys Ser Pro Ala Leu Ser Leu His Ser Ala Thr  
435 440 445

Ser Asp His Gly Tyr Glu Ser Ile Leu Gly Ser Pro Thr Ser Val Ala  
450 455 460

Leu Thr Leu Pro Ala Asp Glu Asp Asp Phe Pro Trp Glu Ser Asn Phe  
465 470 475 480

Asp Glu Leu Phe Pro Ser Leu Ile  
485

&lt;210&gt; 47

&lt;211&gt; 753

&lt;212&gt; DNA

<213> *Drosophila melanogaster*

&lt;400&gt; 47

atgagtcaca aaatcgccgc tgtgtgcctc ttgatgagct gcctgattgc cacggcttat 60

agtgccgcta aggtgccaat ttctatctac tacgagtccc tgtgcccgga cagcgccaag 120

ttcattacgg agcaggtata tccggcgggtg aagggagaac tgcgcgatgt ggtggaactc 180

actttcgtgc cattcggaag gtctcagttc gttaccagg gctccgaagt gacgttcacc 240

tgccaccacg gaccgaacga gtgctatggc aataaggtgc atgcctgcgc catcgagcac 300

attcaggcca actcctatca ggtggagtac acgcgcgagt cgctcacgat ggacttcac 360

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aactgcctaa tgaaggccgg caagaatttc ccggacaacg tctatcccgg ccagcgatgc 420
gcctcggaga accacatcaa taactgggag aacatcaaga cctgtgccaa ctccaccgag 480
ggaagcggttc tgctccggaa ggccggcgaa agcaccatgc ggctcaagga gccactcacc 540
agcgtgcccc ccattctgtt caatgagcaa ttcgacaaga aggtgaatga tcgcgcccag 600
gtgaacttgg tgggcaccat ctgccaatac gtatccgccc cgcagccgcg catctgcaac 660
cagcacaacg gagcatcgac tccatctttg gccagcgtaa gcgccatcct tagctcctg 720
ctgggtcttt ggtttatccg ctccttctac taa 753

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&lt;210&gt; 48

&lt;211&gt; 250

&lt;212&gt; PRT

<213> *Drosophila melanogaster*

&lt;400&gt; 48

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Met Ser His Lys Ile Ala Ala Val Cys Leu Leu Met Ser Cys Leu Ile
1           5           10           15
Ala Thr Ala Tyr Ser Ala Ala Lys Val Pro Ile Ser Ile Tyr Tyr Glu
20           25           30
Ser Leu Cys Pro Asp Ser Ala Lys Phe Ile Thr Glu Gln Val Tyr Pro
35           40           45
Ala Val Lys Gly Glu Leu Arg Asp Val Val Glu Leu Thr Phe Val Pro
50           55           60
Phe Gly Lys Ser Gln Phe Val Thr Gln Gly Ser Glu Val Thr Phe Thr
65           70           75           80
Cys His His Gly Pro Asn Glu Cys Tyr Gly Asn Lys Val His Ala Cys
85           90           95
Ala Ile Glu His Ile Gln Ala Asn Ser Tyr Gln Val Glu Tyr Thr Arg
100          105          110
Glu Ser Leu Thr Met Asp Phe Ile Asn Cys Leu Met Lys Ala Gly Lys
115          120          125
Asn Phe Pro Asp Asn Val Tyr Pro Gly Gln Arg Cys Ala Ser Glu Asn
130          135          140
His Ile Asn Asn Trp Glu Asn Ile Lys Thr Cys Ala Asn Ser Thr Glu
145          150          155          160
Gly Ser Val Leu Leu Arg Lys Ala Gly Glu Ser Thr Met Arg Leu Lys
165          170          175
Glu Pro Leu Thr Ser Val Pro Thr Ile Leu Phe Asn Glu Gln Phe Asp
180          185          190
Lys Lys Val Asn Asp Arg Ala Gln Val Asn Leu Val Gly Thr Ile Cys
195          200          205

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Gln Tyr Val Ser Ala Pro Gln Pro Arg Ile Cys Asn Gln His Asn Gly  
 210 215 220

Ala Ser Thr Pro Ser Leu Ala Ser Val Ser Ala Ile Leu Ser Ser Leu  
 225 230 235 240

Leu Gly Leu Trp Phe Ile Arg Ser Phe Tyr  
 245 250

<210> 49  
 <211> 1365  
 <212> DNA  
 <213> Drosophila melanogaster

<400> 49  
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 aaactggagc aggtggacaa tctgtaccag gagtttgaga ctccggagaa ggccaacaag 120  
 ctgctgaagc tgaagcactt tgagaaattc aatgacacca cagagggcgt ggccgctgca 180  
 acggcgggcg tggagggcaa ggtagccaag ccgctgaaaa agacactcaa gaagctgctc 240  
 gttgacgacg tgcagtcttc gctcttggtt gccgatgcca aactgggcac agccatcaag 300  
 gacaaactgt cggtagagt tgtctgcaac actggcgctc aggagctgat gcgctgtatt 360  
 cgccagcagg cggacagtct gcttggtggt ctgcccagc gtgagatgac cgccatggcc 420  
 ctgggtcttg cccactcctt gtcgcgtac aagcttaagt tctcgcccga caagatcgac 480  
 acaatgattg tgcaggccca gtgcttgctg gatgacctgg acaaggagtt gaacaactac 540  
 atgatgcgtg cagcgagtg gtacggttgg cactttcccg agctgggcaa gattattacc 600  
 gacaacattg ctttcgtgaa gaccatcaag ttggtgggca ccagggataa tatggccaca 660  
 agcgatctgt ccgacattct gccagaagat gtggaggaaa aggtcaagga ggcagctgag 720  
 atctctatgg gtaccgaaat ctccgaggag gatgtgctga acattcagt tctgtgcgac 780  
 gagatcatat cgatcaacga ttaccgcacc cacttgtagc actacttgaa ggccagaatg 840  
 atggccatgg ctccgaattt gacagtgtc gtgggagaca ccgtcggcgc tcgactgatt 900  
 gccatgctg gtcgctgat taacctggcc aagcatccct catctactgt acaaattctg 960  
 ggcgccgaga aagcactctt ccgtgcgctg aagaccaaga aggatactcc aaagtacggt 1020  
 ttgatctatc acgcccagtt ggtgggacag gcaagccaga agaacaaggg caaaatgtcg 1080  
 cgttcactgg ccgcccgaagc gtcgcttgcc acgcgtgttg atgcctttgg cgaagaggct 1140  
 acctttgagc taggagcggc tcacaagggt aaactggagt ctcggtgctg actcctggag 1200  
 gagggcaacc tgcgcaaact ctccggcacc ggcaaggcca aggccaagtt cgagaagtac 1260  
 caggccaaga ggcgaggtgt tcacctacca accagaggcc gacaacacct tgaacgtgaa 1320  
 gaagaagcgc aagcactccg agtccgaaca gcagacgcct gttaa 1365



<210> 50  
 <211> 454  
 <212> PRT  
 <213> *Drosophila melanogaster*

<400> 50

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Met Phe Val Leu Tyr Glu Thr Pro Ala Gly Tyr Ala Ile Phe Lys Leu
1           5           10           15

Leu Asp Glu Lys Lys Leu Glu Gln Val Asp Asn Leu Tyr Gln Glu Phe
          20           25           30

Glu Thr Pro Glu Lys Ala Asn Lys Leu Leu Lys Leu Lys His Phe Glu
          35           40           45

Lys Phe Asn Asp Thr Thr Glu Ala Leu Ala Ala Ala Thr Ala Ala Val
50           55           60

Glu Gly Lys Val Ala Lys Pro Leu Lys Lys Thr Leu Lys Lys Leu Leu
65           70           75           80

Val Asp Asp Val Gln Ser Ser Leu Leu Val Ala Asp Ala Lys Leu Gly
          85           90           95

Thr Ala Ile Lys Asp Lys Leu Ser Val Gln Cys Val Cys Asn Thr Gly
          100          105          110

Val Gln Glu Leu Met Arg Cys Ile Arg Gln Gln Ala Asp Ser Leu Leu
          115          120          125

Gly Gly Leu Pro Lys Arg Glu Met Thr Ala Met Ala Leu Gly Leu Ala
          130          135          140

His Ser Leu Ser Arg Tyr Lys Leu Lys Phe Ser Pro Asp Lys Ile Asp
145           150           155           160

Thr Met Ile Val Gln Ala Gln Cys Leu Leu Asp Asp Leu Asp Lys Glu
          165          170          175

Leu Asn Asn Tyr Met Met Arg Ala Arg Glu Trp Tyr Gly Trp His Phe
          180          185          190

Pro Glu Leu Gly Lys Ile Ile Thr Asp Asn Ile Ala Phe Val Lys Thr
          195          200          205

Ile Lys Leu Val Gly Thr Arg Asp Asn Met Ala Thr Ser Asp Leu Ser
          210          215          220

Asp Ile Leu Pro Glu Asp Val Glu Glu Lys Val Lys Glu Ala Ala Glu
225           230           235           240

Ile Ser Met Gly Thr Glu Ile Ser Glu Glu Asp Val Leu Asn Ile Gln
          245          250          255

Cys Leu Cys Asp Glu Ile Ile Ser Ile Asn Asp Tyr Arg Thr His Leu
          260          265          270

Tyr Asp Tyr Leu Lys Ala Arg Met Met Ala Met Ala Pro Asn Leu Thr
          275          280          285

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Val Leu Val Gly Asp Thr Val Gly Ala Arg Leu Ile Ala His Ala Gly  
 290 295 300

Ser Leu Ile Asn Leu Ala Lys His Pro Ser Ser Thr Val Gln Ile Leu  
 305 310 315 320

Gly Ala Glu Lys Ala Leu Phe Arg Ala Leu Lys Thr Lys Lys Asp Thr  
 325 330 335

Pro Lys Tyr Gly Leu Ile Tyr His Ala Gln Leu Val Gly Gln Ala Ser  
 340 345 350

Gln Lys Asn Lys Gly Lys Met Ser Arg Ser Leu Ala Ala Lys Ala Ser  
 355 360 365

Leu Ala Thr Arg Val Asp Ala Phe Gly Glu Glu Ala Thr Phe Glu Leu  
 370 375 380

Gly Ala Ala His Lys Val Lys Leu Glu Ser Arg Leu Arg Leu Leu Glu  
 385 390 395 400

Glu Gly Asn Leu Arg Lys Leu Ser Gly Thr Gly Lys Ala Lys Ala Lys  
 405 410 415

Phe Glu Lys Tyr Gln Ala Lys Arg Arg Gly Val His Leu Pro Thr Arg  
 420 425 430

Gly Arg Gln His Leu Glu Arg Glu Glu Glu Ala Gln Ala Leu Arg Val  
 435 440 445

Arg Thr Ala Asp Ala Cys  
 450

<210> 51  
 <211> 1218  
 <212> DNA  
 <213> Drosophila melanogaster

<400> 51  
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 caggcagccg cagcagttgt tgcggtcgcg caacagcagc aggctcaagc ccaagcccag 120  
 gctcaggctc aggcacagca gcagcaacag gcgccgcagg tgggtgtccc catgaccccg 180  
 cagcacttga cccacagca gcagcagcag agcacacaga gcatcgccga ctatctggcc 240  
 cagttgctca aggaccgcaa gcaactggcc gccttcccca acgtcttcac ccacgtcgaa 300  
 cgcttgctgg acgaagaaat tgcacgcgtg cgcgcctcac tgttcagat caatggggtc 360  
 aagaaggagc cgctcactct gcccgaaacc gagggctctg tggtgacgat gaacgagaag 420  
 gtttatgtgc cagtcgcga gcatccagat ttcaactttg tcggtcgcat tttgggaccc 480  
 cgtggcatga ccgccaagca attggaacag gagaccggct gcaagattat ggtccgaggc 540  
 aagggttcca tgcgcgacaa gaagaaggag gacgccaacc gtggcaagcc taactgggag 600  
 catctgtccg atgacctgca tgtcctgata accgtcgagg acaccgagaa ccgtgccaca 660

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gtgaagttgg cccaggccgt cgccgaagta cagaagttgc tcgtgccgca agccgaaggc 720
gaagatgagc taaagaaacg tcaactcatg gaattggcga ttattaatgg cacttatagg 780
gacacaacag cgaaatctgt cgcagtgtgc gatgaggagt ggcgccgcct ggttgccgcc 840
tctgatagcc gcctgctgac atccaccggc ctgcccggcc ttgccgccca gatccgtgca 900
cccgccgccg ccccgcttgg cgccccattg atcctgaatc cccggatgac cgtccccaca 960
acggcgggcca gcatattgtc cgcccaggcc gctccgacag ccgccttcga ccagaccggc 1020
catggaatga tcttcgcacc gtacgattat gcgaactacg ccgccttagc cggcaatcct 1080
ctgctcacgg aatatgctga tcatagcgta ggcgccatta agcagcagcg tcgtttggcg 1140
actaaccgcg agcatcccta tcagcgagca acggtcggag tgccagccaa gccggcgggc 1200
ttcattgaga tacagtaa 1218

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<210> 52
<211> 405
<212> PRT
<213> Drosophila melanogaster

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<400> 52
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Met Ser Val Cys Glu Ser Lys Ala Val Val Gln Gln Gln Leu Gln Gln
1           5           10           15
His Leu Gln Gln Gln Ala Ala Ala Ala Val Val Ala Val Ala Gln Gln
20           25           30
Gln Gln Ala Gln Ala Gln Ala Gln Ala Gln Ala Gln Ala Gln Gln Gln
35           40           45
Gln Gln Ala Pro Gln Val Val Val Pro Met Thr Pro Gln His Leu Thr
50           55           60
Pro Gln Gln Gln Gln Gln Ser Thr Gln Ser Ile Ala Asp Tyr Leu Ala
65           70           75           80
Gln Leu Leu Lys Asp Arg Lys Gln Leu Ala Ala Phe Pro Asn Val Phe
85           90           95
Thr His Val Glu Arg Leu Leu Asp Glu Glu Ile Ala Arg Val Arg Ala
100          105          110
Ser Leu Phe Gln Ile Asn Gly Val Lys Lys Glu Pro Leu Thr Leu Pro
115          120          125
Glu Pro Glu Gly Ser Val Val Thr Met Asn Glu Lys Val Tyr Val Pro
130          135          140
Val Arg Glu His Pro Asp Phe Asn Phe Val Gly Arg Ile Leu Gly Pro
145          150          155          160
Arg Gly Met Thr Ala Lys Gln Leu Glu Gln Glu Thr Gly Cys Lys Ile
165          170          175

```

Met Val Arg Gly Lys Gly Ser Met Arg Asp Lys Lys Lys Glu Asp Ala  
 180 185 190

Asn Arg Gly Lys Pro Asn Trp Glu His Leu Ser Asp Asp Leu His Val  
 195 200 205

Leu Ile Thr Val Glu Asp Thr Glu Asn Arg Ala Thr Val Lys Leu Ala  
 210 215 220

Gln Ala Val Ala Glu Val Gln Lys Leu Leu Val Pro Gln Ala Glu Gly  
 225 230 235 240

Glu Asp Glu Leu Lys Lys Arg Gln Leu Met Glu Leu Ala Ile Ile Asn  
 245 250 255

Gly Thr Tyr Arg Asp Thr Thr Ala Lys Ser Val Ala Val Cys Asp Glu  
 260 265 270

Glu Trp Arg Arg Leu Val Ala Ala Ser Asp Ser Arg Leu Leu Thr Ser  
 275 280 285

Thr Gly Leu Pro Gly Leu Ala Ala Gln Ile Arg Ala Pro Ala Ala Ala  
 290 295 300

Pro Leu Gly Ala Pro Leu Ile Leu Asn Pro Arg Met Thr Val Pro Thr  
 305 310 315 320

Thr Ala Ala Ser Ile Leu Ser Ala Gln Ala Ala Pro Thr Ala Ala Phe  
 325 330 335

Asp Gln Thr Gly His Gly Met Ile Phe Ala Pro Tyr Asp Tyr Ala Asn  
 340 345 350

Tyr Ala Ala Leu Ala Gly Asn Pro Leu Leu Thr Glu Tyr Ala Asp His  
 355 360 365

Ser Val Gly Ala Ile Lys Gln Gln Arg Arg Leu Ala Thr Asn Arg Glu  
 370 375 380

His Pro Tyr Gln Arg Ala Thr Val Gly Val Pro Ala Lys Pro Ala Gly  
 385 390 395 400

Phe Ile Glu Ile Gln  
 405

<210> 53  
 <211> 1290  
 <212> DNA  
 <213> *Drosophila melanogaster*

<400> 53  
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 cagacgattg cggaaggtca agctattcca aggggcctgc acgtgcgcat caacctacia 180  
 acggggctca aggaagccaa actcttagac gaaagcgaac gtggcacgtc gctgcagagt 240  
 caaccggatg atcagaatgc tcgggaatct cagcatgaca acgaaccctt ggctctggac 300

tataaaccgg acataatcga ggagtctata cggcgggtca aggagcagaa gaagagctat 360  
gccgagctac gcaaagcgta caaagagttc cagaagaact ttcgcaccga cggagaactg 420  
atcgtccagt taatcgatca gtttcggaac ttcagcagaa cgccgctaga gtcagagatg 480  
cgctccaagc tggactgcct ggaaaatctg gagtatttgc tccatcagat agacaatgcc 540  
ttgatgttca ttgataatgg gggattggat gatgtactac tgcccattgt tgtgaacgat 600  
accagtacat ccctgagagt gtcggccatg cgtgtgttgg gctcgtggc gagcaacaat 660  
cccaaggccc agatcaaggt gttcgaaaag aatttcgggt ctcatctggc tcagattctg 720  
accagttccg gaaatgtcgg tgagatctcc gctgcattgc acgcctttgg agccttggtg 780  
cggaaatttc cgctagccca gcagcgagtg ctttccacct cgggtacaca ggctctgatc 840  
aaggtgctcc agagtcggga tgtggagctg cggagcaagg cgaaggtagt gactctcata 900  
agcgacctag tgctggagaa gcggtcagtg ctggatgtca gcaaagatga tcccgaagcc 960  
tcatccacaa tggcgcaata tgtgctcttg gacttcgagt cgtggctgaa aacgccgggc 1020  
tactgcgcgg cgggtggacac tgtgctaacc aaggagttcc tgctcctcct agagcaaccg 1080  
gaggtggtgg aacagtttgc caccgcattg gagaccaccg aagatatgtg caccagcacg 1140  
tggtcgcaaa gttccggtct caggcatgca ctattaaccg ttcgcaatcg gtatgccaac 1200  
agcacggacg agtaccgact ggaggtgtcc cagatttttg ccaaactgtg cgagagattg 1260  
ttcaacaagc ccaagcacac cgaactgtaa 1290

<210> 54  
<211> 429  
<212> PRT  
<213> *Drosophila melanogaster*

<400> 54

Met Ser Gly Lys Gln Val Val Ile Leu Leu Gly Ser Val Leu Ile Leu  
1 5 10 15

Gly Cys Leu Gln Val Ala Ala Ala Thr Glu Thr Asp Asn Lys Thr Asn  
20 25 30

Asp Phe Val Ala Thr Asp Glu Trp Gln Thr Ile Ala Glu Gly Gln Ala  
35 40 45

Ile Pro Arg Gly Leu His Val Arg Ile Asn Leu Gln Thr Gly Leu Lys  
50 55 60

Glu Ala Lys Leu Leu Asp Glu Ser Glu Arg Gly Thr Ser Leu Gln Ser  
65 70 75 80

Gln Pro Asp Asp Gln Asn Ala Arg Glu Ser His Asp Asp Asn Glu Pro  
85 90 95

Leu Ala Leu Asp Tyr Lys Pro Asp Ile Ile Glu Glu Ser Ile Arg Arg  
 100 105 110  
 Val Lys Glu Gln Lys Lys Ser Tyr Ala Glu Leu Arg Lys Ala Tyr Lys  
 115 120 125  
 Glu Phe Gln Lys Asn Phe Arg Thr Asp Gly Glu Leu Ile Val Gln Leu  
 130 135 140  
 Ile Asp Gln Phe Arg Asn Phe Ser Arg Thr Pro Leu Glu Ser Glu Met  
 145 150 155 160  
 Arg Ser Lys Leu Asp Cys Leu Glu Asn Leu Glu Tyr Leu Leu His Gln  
 165 170 175  
 Ile Asp Asn Ala Leu Met Phe Ile Asp Asn Gly Gly Leu Asp Asp Val  
 180 185 190  
 Leu Leu Pro Ile Val Val Asn Asp Thr Ser Thr Ser Leu Arg Val Ser  
 195 200 205  
 Ala Met Arg Val Leu Gly Ser Leu Ala Ser Asn Asn Pro Lys Ala Gln  
 210 215 220  
 Ile Lys Val Phe Glu Lys Asn Phe Gly Ser His Leu Ala Gln Ile Leu  
 225 230 235 240  
 Thr Ser Ser Gly Asn Val Gly Glu Ile Ser Ala Ala Leu His Ala Phe  
 245 250 255  
 Gly Ala Leu Leu Arg Lys Phe Pro Leu Ala Gln Gln Arg Val Leu Ser  
 260 265 270  
 Thr Ser Gly Thr Gln Ala Leu Ile Lys Val Leu Gln Ser Pro Asp Val  
 275 280 285  
 Glu Leu Arg Ser Lys Ala Lys Val Val Thr Leu Ile Ser Asp Leu Val  
 290 295 300  
 Leu Glu Lys Arg Ser Val Leu Asp Val Ser Lys Asp Asp Pro Glu Ala  
 305 310 315 320  
 Ser Ser Thr Met Ala Gln Tyr Val Leu Leu Asp Phe Glu Ser Trp Leu  
 325 330 335  
 Lys Thr Pro Gly Tyr Cys Ala Ala Val Asp Thr Val Leu Thr Lys Glu  
 340 345 350  
 Phe Leu Leu Leu Leu Glu Gln Pro Glu Val Val Glu Gln Phe Ala Thr  
 355 360 365  
 Ala Leu Glu Thr Thr Glu Asp Met Cys Thr Ser Thr Trp Ser Gln Ser  
 370 375 380  
 Ser Gly Leu Arg His Ala Leu Leu Thr Val Arg Asn Arg Tyr Ala Asn  
 385 390 395 400  
 Ser Thr Asp Glu Tyr Arg Leu Glu Val Ser Gln Ile Leu Ala Lys Leu  
 405 410 415  
 Cys Glu Arg Leu Phe Asn Lys Pro Lys His Thr Glu Leu

420

425

<210> 55  
 <211> 336  
 <212> DNA  
 <213> Drosophila melanogaster

<400> 55  
 atgggtggccg ttaagaaaca aaagaaggct ctggagagca ccaacgcccg tctggcgctg 60  
 gtgatgaagt ccggcaaata ctgcctgggc tacaagcaga ccttgaagac cctgcgccag 120  
 ggcaaggcca aactggtgct catcgccagc aacacgcccg ccctgaggaa gtccgagatc 180  
 gagtactacg ctatgctggc caagactgaa gtccagcact acagcggcac caacatcgag 240  
 ctgggcaccg cctgtggtaa atacttccgc gtgtgcaccc tgtccatcac cgatcctgga 300  
 gattcggaca tcatcgctc gctggagacg gcctaa 336

<210> 56  
 <211> 111  
 <212> PRT  
 <213> Drosophila melanogaster

<400> 56  
 Met Val Ala Val Lys Lys Gln Lys Lys Ala Leu Glu Ser Thr Asn Ala  
 1 5 10 15  
 Arg Leu Ala Leu Val Met Lys Ser Gly Lys Tyr Cys Leu Gly Tyr Lys  
 20 25 30  
 Gln Thr Leu Lys Thr Leu Arg Gln Gly Lys Ala Lys Leu Val Leu Ile  
 35 40 45  
 Ala Ser Asn Thr Pro Ala Leu Arg Lys Ser Glu Ile Glu Tyr Tyr Ala  
 50 55 60  
 Met Leu Ala Lys Thr Glu Val Gln His Tyr Ser Gly Thr Asn Ile Glu  
 65 70 75 80  
 Leu Gly Thr Ala Cys Gly Lys Tyr Phe Arg Val Cys Thr Leu Ser Ile  
 85 90 95  
 Thr Asp Pro Gly Asp Ser Asp Ile Ile Arg Ser Leu Glu Thr Ala  
 100 105 110

<210> 57  
 <211> 822  
 <212> DNA  
 <213> Drosophila melanogaster

<400> 57  
 atggctcact tcgcatgac accaaacata cgtcacaaca acaaaaacaa caacaacaac 60  
 aacgacaaga tgtggcagca tgtgcacaaa tgcaatccgg ttcgcttgcc cgccaagcta 120  
 gacgagcaaa aaatgtttat ttttaacaat attccacaga ttatcatctg tcgtcgtctg 180

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atgcacttcg atgaatgggc gacgcttcct ttcgctcgcc atccgcccgcg atccgctgac      240
gccgcccatt cccggcagcaa gaactcaaac gttgcgaacg gaagcgaaat gcaagtggaa      300
tcgagctata ccaaatatgc cggacgtgtg ccacctttgg acctcaccca ggtgaatggt      360
ggccaagatt tgtggggcgg caatggtggc ggcaataacg catccgccag acgccatctg      420
catcatccct atcaaattgct ggacaagtgc cgcggcggag taaccctgat cagtgcacatca      480
tccgccatct catctacatc caactcctcc gacgacaata acaatcgact gatgagcgct      540
gatgatggca ccaccagtct gctgcatccc ttgggctccg atgggtctgcc tctggatccg      600
cgcgattgga cgcgagcggg tgtctggaaa tggctcatca atatggccgt atccgagggg      660
ttggaggtca ccgccgaact gccacagaaa ttcccatga acggcaaggc attgtgcctg      720
atgagtctcg atatgtacct gtgccgagtt cccgtgggcg gcaagatgct ctaccgcgac      780
ttccgggtgc gactcgcccg agcaatggcc ctgctatcat ag                          822

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<210> 58  
 <211> 273  
 <212> PRT  
 <213> *Drosophila melanogaster*

<400> 58

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Met Ala His Phe Ala Met Thr Pro Asn Ile Arg His Asn Asn Lys Asn
1           5           10           15
Asn Asn Asn Asn Asn Asp Lys Met Trp Gln His Val His Lys Cys Asn
20           25           30
Pro Val Arg Leu Pro Ala Lys Leu Asp Glu Gln Lys Met Phe Ile Phe
35           40           45
Asn Asn Ile Pro Gln Ile Ile Ile Cys Arg Arg Leu Met His Phe Asp
50           55           60
Glu Trp Ala Thr Leu Pro Phe Ala Arg His Pro Pro Arg Ser Ala Asp
65           70           75           80
Ala Ala His Ser Gly Ser Lys Asn Ser Asn Val Ala Asn Gly Ser Glu
85           90           95
Met Gln Val Glu Ser Ser Tyr Thr Lys Tyr Ala Gly Arg Val Pro Pro
100          105          110
Leu Asp Leu Thr Gln Val Asn Gly Gly Gln Asp Leu Trp Gly Gly Asn
115          120          125
Gly Gly Gly Asn Asn Ala Ser Ala Arg Arg His Leu His His Pro Tyr
130          135          140
Gln Met Leu Asp Lys Cys Arg Gly Gly Val Thr Leu Ile Ser Ala Ser
145          150          155          160
Ser Ala Ile Ser Ser Thr Ser Asn Ser Ser Asp Asp Asn Asn Asn Arg

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165	170	175
Leu Met Ser Ala Asp Asp Gly Thr Thr Ser Leu Leu His Pro Leu Gly		
180	185	190
Ser Asp Gly Leu Pro Leu Asp Pro Arg Asp Trp Thr Arg Ala Asp Val		
195	200	205
Trp Lys Trp Leu Ile Asn Met Ala Val Ser Glu Gly Leu Glu Val Thr		
210	215	220
Ala Glu Leu Pro Gln Lys Phe Pro Met Asn Gly Lys Ala Leu Cys Leu		
225	230	235
Met Ser Leu Asp Met Tyr Leu Cys Arg Val Pro Val Gly Gly Lys Met		
245	250	255
Leu Tyr Arg Asp Phe Arg Val Arg Leu Ala Arg Ala Met Ala Leu Leu		
260	265	270

Ser

<210> 59  
 <211> 1341  
 <212> DNA  
 <213> *Drosophila melanogaster*

<400> 59  
 atgcagatct ttgtgaagac tttgaccgga aagaccatca ccctcgaggt agagccctcg 60  
 gacaccattg agaatgtaa ggctaagatc caagacaagg aaggaattcc ccagatcag 120  
 cagcgtctga tcttcgccgg caagcaactg gaagacggac gcaccctgtc cgattacaac 180  
 attcagaagg agtccaccct tcaacttggtc cttcgtctcc gtggtggtat gcagatcttc 240  
 gtgaagactt tgaccggaaa gaccatcacc ctcgaggtag agccatcgga caccattgag 300  
 aataaggagt ccacccttca cttggtcctt cgtctccgtg gtggtatgca gatcttcgtg 360  
 aagactttga ccggaagac catcacctc gaggtagagc catcggaac aattgagaat 420  
 gttaaggcta agatccaaga caaggaggga attccccag atcagcagcg tctgatcttc 480  
 gccggcaagc agcttgagga tggacgcacc ctgtccgatt acaacatcca gaaggagtcc 540  
 acccttcact tggctccttcg tctccgtggt ggtatgcaga tcttcgtgaa gactttgacc 600  
 ggaaagacca tcaccctcga ggtagagcct tcggacacca ttgagaatgt taaggctaag 660  
 atccaagaca aggagggaat tccccagat cagcagcgtc tgatcttcgc cggcaagcag 720  
 cttgaggatg gacgcaccct gtccgattac aacattcaga aggagtccac ccttcacttg 780  
 gtccttcgtc ttcgtggtgg tatgcagatc ttcgtgaaga ctttgaccgg aaagaccatc 840  
 accctcgagg tagagccatc ggacacaatt gagaatgtta aggctaagat ccaagacaag 900  
 gagggaaattc cccagatca gcagcgtctg atcttcgccg gcaagcagct tgaggatgga 960

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cgccacctgt cggattacaa catccagaag gagtccaccc ttcacttggt ccttcgtctc 1020
cgtggttgga tgcagatctt cgccaagatt caagataagg agggaatccc cccagatcag 1080
cagcgtctga tcttcgccgg caagcagctt gaggatggac gcacctgtgc cgattacaac 1140
atccagaagg agtccaccct tcaacttggtc cttcgtctcc gtggtggtat gcagatcttc 1200
gtgaagactt tgaccggaaa gaccatcacc ctcgaggtag agccttcgga caccattgag 1260
aatgttaagg ctaagatcca agacaaggag ggaattcccc cagatcagca gcagtctgat 1320
cttcgccggc aagcagcttg a 1341

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<210> 60
<211> 446
<212> PRT
<213> Drosophila melanogaster

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<400> 60

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Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu
1           5           10           15
Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp
20           25           30
Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys
35           40           45
Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu
50           55           60
Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe
65           70           75           80
Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser
85           90           95
Asp Thr Ile Glu Asn Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu
100          105          110
Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile
115          120          125
Thr Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys
130          135          140
Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe
145          150          155          160
Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile
165          170          175
Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met
180          185          190
Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val
195          200          205

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Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys  
 210 215 220  
 Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln  
 225 230 235 240  
 Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser  
 245 250 255  
 Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val  
 260 265 270  
 Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp  
 275 280 285  
 Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro  
 290 295 300  
 Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly  
 305 310 315 320  
 Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu  
 325 330 335  
 Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Ala Lys Ile Gln Asp  
 340 345 350  
 Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys  
 355 360 365  
 Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu  
 370 375 380  
 Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe  
 385 390 395 400  
 Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser  
 405 410 415  
 Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile  
 420 425 430  
 Pro Pro Asp Gln Gln Gln Ser Asp Leu Arg Arg Gln Ala Ala  
 435 440 445

&lt;210&gt; 61

&lt;211&gt; 1884

&lt;212&gt; DNA

&lt;213&gt; Drosophila melanogaster

&lt;400&gt; 61

atgaaataca tcctggtaac tgggtggcgtc attagtggcg tgggaaaagg agtgattgcc 60  
 tcctcgttcg gaacgctttt gaaatcctgt ggtctggatg taacctcgat caagattgac 120  
 ccctatatca atatagatgc tggaaccttt tcgccttatg agcatggcga gggtttacgtt 180  
 ttggacgatg gcgccgaggt ggatctggat ctgggaaact atgaacggtt tttggatggt 240  
 accctgcacg gggacaacaa cataaccacc ggaaaaattt acaagttggt cattgagaag 300

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gagcgcactg gcgagtaactt gggcaaaacg gttcaagttg tcccacacat cactgatgcc 360
attcaggaat ggggtggagcg cgtggcccag acaccggttc agggatcttc aaagccacag 420
gtgtgcatcg tggaattggg aggaacgatt ggtgacatcg aaggcatgcc tttcgtagag 480
gccttccgtc agtttcagtt ccgcgtaaag agagagaact tctgtttggc ccatgtgtcg 540
ctggttccgt tgccaaaggc taccggagaa cccaagacca agcccacaca aagttcggtc 600
agagaactga gaggatgtgg cctgagtccc gatttgattg tctgccgac ggagaaaccc 660
attggactgg aggtcaagga gaagatcagc aacttttgtc atgtggggcc ggatcaggtg 720
atatgcatcc acgatttgaa ctccatttat catgttccgc tgctgatgga gcagaatggt 780
gttattgaat acctaaatga ggcctacag cttaatatcg acatgagcaa gaggaccaa 840
tgcttgacgc aatggcgaga tttggcgct cgaacggaga ccgttcgccg tgaagtttgc 900
atcgccgctg tgggaaagta caccaagttc acggattcgt acgcctccgt agttaaagcc 960
ctgcaacatg ccgccctggc agtgaatcgc aaactggaac tggctcttat cgagtcgtgc 1020
ctgctggagg aggaaacttt gcattctgag ccgagcaagt accacaagga gtggcagaag 1080
ctatgcgata gccatggcat cctagtcccc ggtggattcg gttcccgtgg aatggagggc 1140
aagattcgtg catgccaatg ggcgcgagag aatcaaaagc cattgcttgg catctgcttg 1200
ggtctgcaag cggcggtcat tgaattcgca cgaaataaac ttggtctcaa ggatgcaaac 1260
accacagaaa tcgatccgaa cacagcta at gccttgggtca tcgatatgcc agagcatcac 1320
acgggtcaat tgggcggcac tatgcgcttg ggcaagcgaa taactgtttt ctctgatggt 1380
cctagtgtca ttcgccagtt gtatggcaat ccgaaaagcg tgcaggagcg tcatcggcat 1440
cgttacgagg ttaatcccaa atacgtgcat ctgctggaag agcaaggcat gcgatttgtg 1500
ggcacccgacg tcgacaaaac taggatggaa atcattgagc tcagcgggtca tccctacttt 1560
gttgccaccc aatatcatcc agagtaacttg tcgcggcctc tgaagccgtc gcctcctttc 1620
ctcggcctga tcctggcctc agtggatcga ttgaaccaat atattcagcg cggttgccgc 1680
ctgtcgcccc gccagctatc cgacgcatcc tcggatgagg aggacagtgt tgtgggcttg 1740
gccggagcaa caaatcgct gagctccttg aaaattccca ttacaccac aaatggaata 1800
tcaaaaagtt gcaatggtag cataagcact tccgacagcg aaggtgcctg cggaggcggt 1860
gacctaacca atggccataa gtaa 1884

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<210> 62
<211> 627
<212> PRT
<213> Drosophila melanogaster
<400> 62

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Met Lys Tyr Ile Leu Val Thr Gly Gly Val Ile Ser Gly Val Gly Lys  
 1 5 10 15  
 Gly Val Ile Ala Ser Ser Phe Gly Thr Leu Leu Lys Ser Cys Gly Leu  
 20 25 30  
 Asp Val Thr Ser Ile Lys Ile Asp Pro Tyr Ile Asn Ile Asp Ala Gly  
 35 40 45  
 Thr Phe Ser Pro Tyr Glu His Gly Glu Val Tyr Val Leu Asp Asp Gly  
 50 55 60  
 Ala Glu Val Asp Leu Asp Leu Gly Asn Tyr Glu Arg Phe Leu Asp Val  
 65 70 75 80  
 Thr Leu His Arg Asp Asn Asn Ile Thr Thr Gly Lys Ile Tyr Lys Leu  
 85 90 95  
 Val Ile Glu Lys Glu Arg Thr Gly Glu Tyr Leu Gly Lys Thr Val Gln  
 100 105 110  
 Val Val Pro His Ile Thr Asp Ala Ile Gln Glu Trp Val Glu Arg Val  
 115 120 125  
 Ala Gln Thr Pro Val Gln Gly Ser Ser Lys Pro Gln Val Cys Ile Val  
 130 135 140  
 Glu Leu Gly Gly Thr Ile Gly Asp Ile Glu Gly Met Pro Phe Val Glu  
 145 150 155 160  
 Ala Phe Arg Gln Phe Gln Phe Arg Val Lys Arg Glu Asn Phe Cys Leu  
 165 170 175  
 Ala His Val Ser Leu Val Pro Leu Pro Lys Ala Thr Gly Glu Pro Lys  
 180 185 190  
 Thr Lys Pro Thr Gln Ser Ser Val Arg Glu Leu Arg Gly Cys Gly Leu  
 195 200 205  
 Ser Pro Asp Leu Ile Val Cys Arg Ser Glu Lys Pro Ile Gly Leu Glu  
 210 215 220  
 Val Lys Glu Lys Ile Ser Asn Phe Cys His Val Gly Pro Asp Gln Val  
 225 230 235 240  
 Ile Cys Ile His Asp Leu Asn Ser Ile Tyr His Val Pro Leu Leu Met  
 245 250 255  
 Glu Gln Asn Gly Val Ile Glu Tyr Leu Asn Glu Arg Leu Gln Leu Asn  
 260 265 270  
 Ile Asp Met Ser Lys Arg Thr Lys Cys Leu Gln Gln Trp Arg Asp Leu  
 275 280 285  
 Ala Arg Arg Thr Glu Thr Val Arg Arg Glu Val Cys Ile Ala Val Val  
 290 295 300  
 Gly Lys Tyr Thr Lys Phe Thr Asp Ser Tyr Ala Ser Val Val Lys Ala  
 305 310 315 320

Leu Gln His Ala Ala Leu Ala Val Asn Arg Lys Leu Glu Leu Val Phe  
 325 330 335  
 Ile Glu Ser Cys Leu Leu Glu Glu Glu Thr Leu His Ser Glu Pro Ser  
 340 345 350  
 Lys Tyr His Lys Glu Trp Gln Lys Leu Cys Asp Ser His Gly Ile Leu  
 355 360 365  
 Val Pro Gly Gly Phe Gly Ser Arg Gly Met Glu Gly Lys Ile Arg Ala  
 370 375 380  
 Cys Gln Trp Ala Arg Glu Asn Gln Lys Pro Leu Leu Gly Ile Cys Leu  
 385 390 395 400  
 Gly Leu Gln Ala Ala Val Ile Glu Phe Ala Arg Asn Lys Leu Gly Leu  
 405 410 415  
 Lys Asp Ala Asn Thr Thr Glu Ile Asp Pro Asn Thr Ala Asn Ala Leu  
 420 425 430  
 Val Ile Asp Met Pro Glu His His Thr Gly Gln Leu Gly Gly Thr Met  
 435 440 445  
 Arg Leu Gly Lys Arg Ile Thr Val Phe Ser Asp Gly Pro Ser Val Ile  
 450 455 460  
 Arg Gln Leu Tyr Gly Asn Pro Lys Ser Val Gln Glu Arg His Arg His  
 465 470 475 480  
 Arg Tyr Glu Val Asn Pro Lys Tyr Val His Leu Leu Glu Glu Gln Gly  
 485 490 495  
 Met Arg Phe Val Gly Thr Asp Val Asp Lys Thr Arg Met Glu Ile Ile  
 500 505 510  
 Glu Leu Ser Gly His Pro Tyr Phe Val Ala Thr Gln Tyr His Pro Glu  
 515 520 525  
 Tyr Leu Ser Arg Pro Leu Lys Pro Ser Pro Pro Phe Leu Gly Leu Ile  
 530 535 540  
 Leu Ala Ser Val Asp Arg Leu Asn Gln Tyr Ile Gln Arg Gly Cys Arg  
 545 550 555 560  
 Leu Ser Pro Arg Gln Leu Ser Asp Ala Ser Ser Asp Glu Glu Asp Ser  
 565 570 575  
 Val Val Gly Leu Ala Gly Ala Thr Lys Ser Leu Ser Ser Leu Lys Ile  
 580 585 590  
 Pro Ile Thr Pro Thr Asn Gly Ile Ser Lys Ser Cys Asn Gly Ser Ile  
 595 600 605  
 Ser Thr Ser Asp Ser Glu Gly Ala Cys Gly Gly Val Asp Pro Thr Asn  
 610 615 620  
 Gly His Lys  
 625

&lt;210&gt; 63

<211> 1905  
 <212> DNA  
 <213> *Drosophila melanogaster*

<400> 63  
 atgaactcca tgaaggtggc catgcagaac tttagccatc gccagcatcc cgccgtgacg 60  
 ataacgagcg ccgacggcac gcaatcaacg gcaaagagca agtaciaaaga cggcagtgcc 120  
 catccgcac c aaggcagcga cgcgcagtat taccacacgg tgacggcggt gcgtccaaac 180  
 tcttcccaac ggtcgccgat gaccaaggtc atggatctgt tccggcatcg atccagctcg 240  
 gttgtcagcg aagccgacaa acgcaaagcg gctcacatgc gtcgtgcctc cgcggtattg 300  
 gagaaacgtc gtgcatcagt tgggtgccga ggtcgaggac tgcgagggga tggactttg 360  
 gatccacacc atgcagccat cctcttcaga gactcacgag ggttgccctgt cgctgatccg 420  
 ttcctagaga aagtaaactc atcagatctg gaagaggacg actcacagat cttcgtgaag 480  
 ttctttcgtt ttcacaagtg ctatgatctg ataccacact ccgccaagtt ggttgtcttc 540  
 gacacccagc ttcttgtaaa gaaggccttc tacgccctcg tctacaacgg tgtgcgagcg 600  
 gcaccgctct gggattcgga gaagcaacag ttcgtgggca tgctaaccat cacggacttt 660  
 atcaagatcc tgcaaagtga ttacaaatcg ccaaagcgt ccatggagca gctggaagag 720  
 cacaaactgg acacgtggcg gagcgtgctg cacaaccagg tgatgccgtt ggtcagcatc 780  
 ggaccggatg cgtccctcta cgatgccatc aaaattctca tccacagccg catacatcg 840  
 ctgcccgtca tcgatccggc gaccggcaat gtcctctaca tctgacaca taaacgcata 900  
 cttaggttcc ttttctata cattaatgaa ttaccaaagc ccggtacat gcaaaaaagt 960  
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 atcatcacgg cgctcaagaa atttgtggag cgacgagtct cagccctgcc actagtggat 1080  
 tccgatggtc gcctcggtga catttacgca aagtttgatg tgattaatct cgccgccgag 1140  
 aaaacctaca acgatctcga tgtttcgctg cgcaaagcca acgagcaccg gaacgagtgg 1200  
 ttcgagggcg tgcagaagtg caatctggac gaatcgctct acacgatcat ggaacgaatc 1260  
 gtccgcgccg aagtacatcg actggtggtg gtcgacgaga atcgcaaagt gatcggcatt 1320  
 atctcgctgt ccgatatact gctctacctc gtcctgcgac caagcggatga aggcgtcggt 1380  
 ggctcggaga gctcattgcg tgcgtccgat cccgttctgc tgcgcaaagt ggctgaggtt 1440  
 gaaataccag cgacagccgc agcggcgacg acaacaaccc cgcctcgag tccatcggcc 1500  
 ggatccggca atcgagcct gatcgaggac ataccgaag aggagacggc gccggcgagg 1560  
 agcgacgatg ccgacagtga taacaataag tccgccagtg aggataaagc caacaataac 1620  
 cagcacgacc agacgacgac ggctgcgaca gctaattggtg atagcaacaa cagccccgta 1680

gaagtgtcct ttgccgatga ggcgagaggaa gaagaagctg ccgaccaggt cgagcgagc 1740  
aattgtgatg atgatgacca gccagcggtta gcggagattg agcgcaagaa tgcacgatg 1800  
gacgacgacg aggacgatgg gatgagcagc gccgtgtccg ctgcctccgc tttggggccag 1860  
tcactgacgc ccgcgggcgca agaaatggcg ttggttagtg aataa 1905

<210> 64  
<211> 634  
<212> PRT  
<213> *Drosophila melanogaster*  
<400> 64

Met Asn Ser Met Lys Val Ala Met Gln Asn Phe Ser His Arg Gln His  
1 5 10 15  
Pro Ala Val Thr Ile Thr Ser Ala Asp Gly Thr Gln Ser Thr Ala Lys  
20 25 30  
Ser Lys Tyr Lys Asp Gly Ser Ala His Pro His Gln Gly Ser Asp Ala  
35 40 45  
Gln Tyr Tyr His Thr Val Thr Ala Val Arg Pro Asn Ser Ser Gln Arg  
50 55 60  
Ser Pro Met Thr Lys Val Met Asp Leu Phe Arg His Arg Ser Ser Ser  
65 70 75 80  
Val Val Ser Glu Ala Asp Lys Arg Lys Ala Ala His Met Arg Arg Ala  
85 90 95  
Ser Ala Asp Leu Glu Lys Arg Arg Ala Ser Val Gly Ala Ala Gly Arg  
100 105 110  
Gly Leu Arg Gly Asp Gly Thr Leu Asp Pro His His Ala Ala Ile Leu  
115 120 125  
Phe Arg Asp Ser Arg Gly Leu Pro Val Ala Asp Pro Phe Leu Glu Lys  
130 135 140  
Val Asn Leu Ser Asp Leu Glu Glu Asp Asp Ser Gln Ile Phe Val Lys  
145 150 155 160  
Phe Phe Arg Phe His Lys Cys Tyr Asp Leu Ile Pro Thr Ser Ala Lys  
165 170 175  
Leu Val Val Phe Asp Thr Gln Leu Leu Val Lys Lys Ala Phe Tyr Ala  
180 185 190  
Leu Val Tyr Asn Gly Val Arg Ala Ala Pro Leu Trp Asp Ser Glu Lys  
195 200 205  
Gln Gln Phe Val Gly Met Leu Thr Ile Thr Asp Phe Ile Lys Ile Leu  
210 215 220  
Gln Met Tyr Tyr Lys Ser Pro Asn Ala Ser Met Glu Gln Leu Glu Glu  
225 230 235 240



His Lys Leu Asp Thr Trp Arg Ser Val Leu His Asn Gln Val Met Pro  
 245 250 255  
 Leu Val Ser Ile Gly Pro Asp Ala Ser Leu Tyr Asp Ala Ile Lys Ile  
 260 265 270  
 Leu Ile His Ser Arg Ile His Arg Leu Pro Val Ile Asp Pro Ala Thr  
 275 280 285  
 Gly Asn Val Leu Tyr Ile Leu Thr His Lys Arg Ile Leu Arg Phe Leu  
 290 295 300  
 Phe Leu Tyr Ile Asn Glu Leu Pro Lys Pro Ala Tyr Met Gln Lys Ser  
 305 310 315 320  
 Leu Arg Glu Leu Lys Ile Gly Thr Tyr Asn Asn Ile Glu Thr Ala Asp  
 325 330 335  
 Glu Thr Thr Ser Ile Ile Thr Ala Leu Lys Lys Phe Val Glu Arg Arg  
 340 345 350  
 Val Ser Ala Leu Pro Leu Val Asp Ser Asp Gly Arg Leu Val Asp Ile  
 355 360 365  
 Tyr Ala Lys Phe Asp Val Ile Asn Leu Ala Ala Glu Lys Thr Tyr Asn  
 370 375 380  
 Asp Leu Asp Val Ser Leu Arg Lys Ala Asn Glu His Arg Asn Glu Trp  
 385 390 395 400  
 Phe Glu Gly Val Gln Lys Cys Asn Leu Asp Glu Ser Leu Tyr Thr Ile  
 405 410 415  
 Met Glu Arg Ile Val Arg Ala Glu Val His Arg Leu Val Val Val Asp  
 420 425 430  
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&lt;211&gt; 24

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&lt;213&gt; Artificial/Unknown

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&lt;211&gt; 28

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(54) Title: NUCLEIC ACID SEQUENCES FROM DROSOPHILA MELANOGASTER THAT ENCODE PROTEINS ESSEN-  
TIAL FOR LARVAL VIABILITY AND USES THEREOF

(57) Abstract: Nucleotide sequences are isolated from *Drosophila melanogaster* that code for proteins essential for larval viability. These proteins are useful for discovering new insecticides based on the essentiality of the nucleotide sequences for *Drosophila* larval viability. Further provided are recombinant proteins and methods for identifying inhibitors to these proteins. Protein inhibitors active in the methods disclosed herein are useful as insecticidal, ectoparasiticide, antiparasitic, anthelmintic and acaricidal agents.

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